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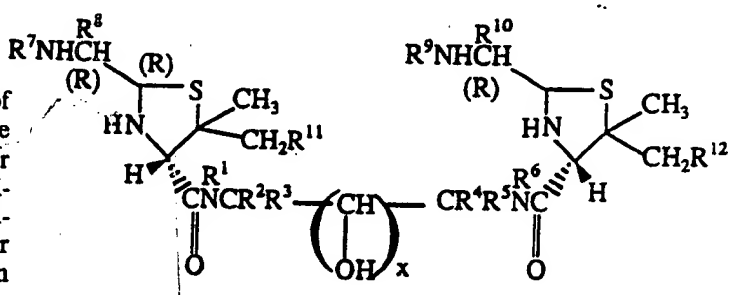
(54) Title: THIAZOLIDINE DERIVATIVES AND THEIR USE IN THERAPY

(57) Abstract

The present invention provides compounds of formula (I), wherein x is zero, 1 or 2; R^1 and R^6 are each independently hydrogen, C_{1-4}alkyl or CH_2C_{1-3}alkyl where the C_{1-3}alkyl portion is substituted by OH; R^2, R^3, R^4 and R^5 are each independently hydrogen, methyl, ethyl, CH_2OH, CH_2NH_2 or COOH when x is zero, or R^2, R^3, R^4 and R^5 are each independently hydrogen, methyl or CH_2OH when x is 1 or 2; R^7 and R^9 are each independently hydrogen, C_{1-10}alkyl, C_{3-8}cycloalkyl, ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, COAr, COHet, $COCH_2R^{13}$, COCH(OH)Ar, COCH(OH)Het, COCH=CHPh, COR^{14}, CO_2CH_2Ar, CO_2CH_2Het, SO_2Ar, SO_2Het, $SO_2CH_2R^{15}$, $SO_2CH=CHPh$ or SO_2R^{16}[where R^{13} and R^{15} each independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, aryloxy, heteroaryloxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, $(CH_2)_nCO_2R^{17}$ (where n is zero or 1 and R^{17} is hydrogen or C_{1-6}alkyl), $(CH_2)_mNR^{18}R^{19}$ (where m is zero, 1, 2, 3, 4 or 5 and R^{18} and R^{19} are each independently hydrogen or C_{1-4}alkyl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group), and R^{14} and R^{16} each independently represent C_{3-8}cycloalkyl substituted by phenyl]; R^9 and R^{10} are each independently hydrogen, C_{1-6}alkyl, $COOR^{20}$ (where R^{20} is hydrogen, C_{1-6}alkyl or ArC_{1-4}alkyl) or $CR^{21}R^{22}$[where R^{21} is hydrogen or C_{1-4}alkyl and R^{22} is hydrogen, OH, aryl, heteroaryl, ArC_{1-4}alkyl (wherein the C_{1-4}alkyl portion is optionally substituted by hydroxymethyl), $HetC_{1-4}$alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, $(CH_2)_pR^{23}$ (where p is zero or 1 and R^{23} is CF_3 or CO_2R^{24} where R^{24} is hydrogen or C_{1-6}alkyl), $(CH_2)_qNR^{25}R^{26}$ (where q is zero, 1, 2, 3, 4, or 5 and R^{25} and R^{26} are each independently hydrogen, C_{1-4}alkyl or aryl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group), $CHArCO_2R^{27}$, $CHHet\,CO_2R^{28}$ (where R^{27} and R^{28} are each independently hydrogen or C_{1-6}alkyl) or C_{1-6}alkyl optionally substituted by OH, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group]; R^{11} and R^{12} are each independently hydrogen, hydroxy or acetoxy; and physiologically acceptable salts and solvates thereof. Also described are the use of the compounds as antiviral agents, pharmaceutical compositions containing them and methods for their preparation.



(I)

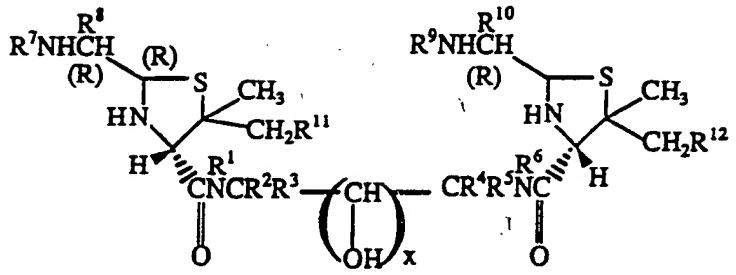
Thiazolidine derivatives and their use in therapy.

The present invention relates to therapeutically active thiazolidine derivatives, processes for the manufacture of said compounds, pharmaceutical formulations containing said compounds and the use of said compounds in chemotherapy, more particularly in the therapy of viral infections.

Retroviruses, that is, viruses within the family of Retroviridae, are a class of viruses which transport their genetic material as ribonucleic acid rather than deoxyribonucleic acid. Their presence has been associated with a wide range of diseases in humans and animals, and they are believed to be the causative agents in pathological states associated with many viruses including human immunodeficiency virus (HIV-1, HIV-2), the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. A common feature of retrovirus replication is the extensive post-translational processing of precursor polyproteins by a virally encoded protease to generate mature viral proteins required for virus assembly and function. The proteolytic activity provided by the viral protease in processing the polyproteins cannot be provided by the host cells and is essential to the life cycle of the retrovirus. It has been demonstrated that retroviruses which lack the protease or contain a mutated form of it lack infectivity [cf. S. Crawford et al., J. Virol., 53, 899-907 (1985)]. Inhibition of retroviral protease, therefore, presents a method of therapy for retroviral disease.

We have now found a novel group of compounds which are useful in the therapy of viral infections. More particularly, the compounds of the present invention inhibit proteases of retroviral origin and are therefore useful in the treatment of infections associated with retroviruses, especially AIDS and related conditions such as AIDS related complex (ARC) and lymphadenopathy.

Thus, in a first aspect, the present invention provides compounds of formula (I)



(I)

wherein :

x is zero, 1 or 2;

R^1 and R^6 are each independently hydrogen, C_{1-4}alkyl or CH_2C_{1-3}alkyl where the C_{1-3}alkyl portion is substituted by OH;

R^2, R^3, R^4 and R^5 are each independently hydrogen, methyl, ethyl, CH_2OH, CH_2NH_2 or COOH when x is zero, or R^2, R^3, R^4 and R^5 are each independently hydrogen, methyl or CH_2OH when x is 1 or 2;

R^7 and R^9 are each independently hydrogen, C_{1-10}alkyl, C_{3-8}cycloalkyl, ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, COAr, COHet, $COCH_2R^{13}$, COCH(OH)Ar, COCH(OH)Het, COCH=CHPh, COR^{14}, CO_2CH_2Ar, CO_2CH_2Het, SO_2Ar, SO_2Het, $SO_2CH_2R^{15}$, $SO_2CH=CHPh$ or SO_2R^{16} [where R^{13} and R^{15} each independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, aryloxy, heteroaryloxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, $(CH_2)_nCO_2R^{17}$ (where n is zero or 1 and R^{17} is hydrogen or C_{1-6}alkyl), $(CH_2)_mNR^{18}R^{19}$ (where m is zero, 1, 2, 3, 4 or 5 and R^{18} and R^{19} are each independently hydrogen or C_{1-4}alkyl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group), and R^{14} and R^{16} each independently represent C_{3-8}cycloalkyl substituted by phenyl];

R^8 and R^{10} are each independently hydrogen, C_{1-6}alkyl, $COOR^{20}$ (where R^{20} is hydrogen, C_{1-6}alkyl or ArC_{1-4}alkyl) or $CONR^{21}R^{22}$ [where R^{21} is hydrogen or C_{1-4}alkyl and R^{22} is hydrogen, OH, aryl, heteroaryl, ArC_{1-4}alkyl (wherein the C_{1-4}alkyl portion is optionally substituted by hydroxymethyl),

$HetC_{1-4}alkyl$, $C_{3-8}cycloalkyl$, $C_{3-8}cycloalkylC_{1-4}alkyl$, $(CH_2)_pR^{23}$ (where p is zero or 1 and R^{23} is CF_3 or CO_2R^{24} where R^{24} is hydrogen or $C_{1-6}alkyl$), $(CH_2)qNR^{25}R^{26}$ (where q is zero, 1, 2, 3, 4 or 5 and R^{25} and R^{26} are each independently hydrogen, $C_{1-4}alkyl$ or aryl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group), $CHArCO_2R^{27}$, $CHHetCO_2R^{28}$ (where R^{27} and R^{28} are each independently hydrogen or $C_{1-6}alkyl$) or $C_{1-6}alkyl$ optionally substituted by OH, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group];

R^{11} and R^{12} are each independently hydrogen, hydroxy or acetoxy;

and physiologically acceptable salts and solvates thereof.

Suitable physiologically acceptable salts of the compounds of formula (I) include acid addition salts formed with organic or inorganic acids [for example, hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, lactates, tartrates, fumarates and maleates] and inorganic base salts such as alkali metal salts (for example sodium salts). The solvates may, for example, be hydrates.

Other salts which are not physiologically acceptable may be useful in the preparation of compounds of formula (I) and these form a further aspect of the invention.

In formula (I) hereinabove the ring carbon atom carrying the group R^7NHCHR^8-, the carbon atom carrying the groups R^7NH- and R^8 and the carbon atom carrying the groups R^9NH- and R^{10} are each in the R configuration whereas the configuration at the carbon atom carrying the group R^9NHCHR^{10}- is not specified. It is to be understood that the present invention encompasses the individual diastereoisomers of the compounds of formula (I) as well as wholly or partially racemic mixtures thereof. However, particularly preferred compounds of formula (I) are those isomers in which the ring carbon atom carrying the group R^9NHCHR^{10}- is also in the R configuration.

As used herein, the term 'alkyl' as a group or part of a group means a straight or branched chain alkyl group, for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl or t-butyl group. The term 'C_{3-8}cycloalkyl' as a group or part of a group includes, for example, cyclopropyl, cyclopentyl and cyclohexyl. The terms 'aryl' and 'Ar', as a group or part of a group respectively, mean a phenyl or naphthyl group optionally substituted by one or more suitable substituents. The terms 'heteroaryl' and 'Het', as a group or part of a group respectively, mean an optionally fused 5- or 6-membered heterocyclic group containing one or more heteroatoms selected from S, N and O and optionally substituted by one or more suitable substituents. Suitable substituents referred to above within the definitions of 'aryl', 'Ar', 'heteroaryl' and 'Het' include halogen, C_{1-6}alkyl, a group $(CH_2)_rR^{29}$ [where r is zero, 1, 2, 3 or 4 and R^{29} is selected from OH, C_{1-3}alkoxy, CF_3, CN, NO_2, heteroaryl, CO_2R^{30} (where R^{30} is hydrogen or C_{1-6}alkyl), $CONR^{31}R^{32}$, $SO_2NR^{31}R^{32}$ or $NR^{31}R^{32}$ (where R^{31} and R^{32} each independently represent hydrogen, C_{1-4}alkyl or phenyl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group)], phenyl, phenoxy and phenylC_{1-4}alkyl (such phenyl, phenoxy and phenylC_{1-4}alkyl substituents themselves optionally substituted in the phenyl ring by halogen, C_{1-3}alkyl, C_{1-3}alkoxy or CF_3). Examples of heterocyclic ring systems include thienyl, furyl, pyridyl, pyrrolyl, isothiazolyl, thiadiazolyl, oxazolyl, benzothienyl, benzofuryl, indolyl, quinolyl, thiazolyl, isoxazolyl, imidazolyl, pyrazolyl, 1,2,4-triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, pyrimidinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, cinnolinyl, benzoxazolyl and benzimidazolyl. The term 'halogen' means fluorine, chlorine, bromine or iodine. The term 'saturated heterocyclic amino group' means a nitrogen linked cyclic amine group having 5, 6, 7 or 8 ring members and optionally containing in the ring -O- or $-NR^{33}-$ (where R^{33} is hydrogen, C_{1-4}alkyl, aryl or ArC_{1-4}alkyl). The saturated heterocyclic amino group may for example have 5, 6 or 7 ring members and includes as examples pyrrolidino, piperidino, morpholino, piperazino, N-phenylpiperazino, homomorpholino and hexamethyleneimino.

Specific examples of the groups 'aryl' and 'Ar' include phenyl or phenyl substituted by F, Cl, di-Cl, OH, methyl, methoxy, CF_3, NO_2, CH_2OH, CO_2H, CO_2Bu-t, $(CH_2)_rNR^{31}R^{32}$ (where r is zero or 1 and R^{31} and R^{32} each independently represent hydrogen or C_{1-4}alkyl or together with the nitrogen atom to which they are attached form a 5, 6 or 7 membered saturated heterocyclic amino group), phenyl or benzyl, and naphthyl or naphthyl substituted by ethoxy.

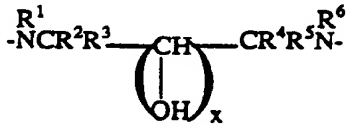
Specific examples of the groups 'heteroaryl' and 'Het' include 2, 3 or 4-pyridyl, 4-imidazolyl, 2 or 3-thienyl and 5-methyl-3-phenyl-4-isoxazolyl.

R^1 and R^6 preferably independently represent hydrogen atoms or methyl groups.

R^3, R^4 and R^5 preferably represent hydrogen atoms.

R^2 preferably represents a hydrogen atom or a methyl, CH_2OH or COOH group when x is zero, and R^2 preferably represents a hydrogen atom when x is 1 or 2.

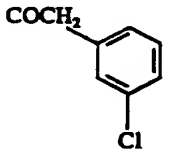
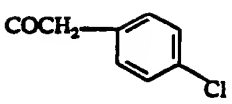
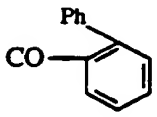
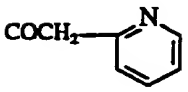
The group



may particularly represent a group selected from $-NHCH_2CH_2NH-$, $-NHCHMeCH_2NH-$, $-NMeCH_2CH_2NMe-$, $-NHCH(CH_2OH)CH_2NH-$, $-NHCH(COOH)CH_2NH-$, $-NHCH_2CH(OH)CH_2NH-$ and $-NHCH_2CH(OH)CH(OH)CH_2NH-$.

R^7 and R^9 preferably independently represent a group selected from COAr (where Ar is biphenyl), $COCH_2R^{13}$ (where R^{13} is C_{1-6}alkyl, for example C_{1-4}alkyl such as isopropyl; aryl, for example phenyl optionally substituted by chlorine; heteroaryl, for example pyridyl; aryloxy, for example phenoxy; or ArC_{1-4}alkyl, for example $ArCH_2$ such as benzyl) or COR^{14} (where R^{14} is cyclopropyl substituted by phenyl).

Compounds in which R^7 and R^9 independently represent $COCH_2Ph$,

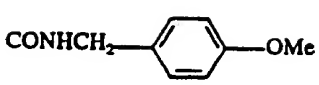

, $COCH_2OPh$, $CO(CH_2)_2Ph$ or

$COCH_2Pr$-i .

are particularly preferred.

R^8 and R^{10} preferably independently represent a group $CONR^{21}R^{22}$ where R^{21} and R^{22} are as defined hereinabove. Such compounds in which R^{21} is hydrogen and R^{22} is a group selected from ArC_{1-4}alkyl (e.g. ArC_{1-2}alkyl where Ar is phenyl optionally substituted by CF_3, methoxy, $NR^{31}R^{32}$ where R^{31} and R^{32} each independently represent methyl or ethyl or together with the nitrogen atom to which they are attached form a pyrrolidino group, Cl, di-Cl or CO_2R^{30} where R^{30} is hydrogen or C_{1-4}alkyl e.g. t-butyl), $HetC_{1-4}$alkyl (e.g. $HetC_{1-2}$alkyl where Het is pyridyl, e.g. 2-pyridyl), C_{3-8}cycloalkylmethyl (e.g. cyclohexylmethyl) or CH_2CF_3 or R^{21} is hydrogen or methyl and R^{22} is methyl or ethyl or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a piperidino group are particularly preferred.

R^8 and R^{10} may particularly independently represent $CONHCH_2Ph$, $CONHCH_2CH_3$, $CONHCH_2CH_2Ph$, $CONMe_2$,



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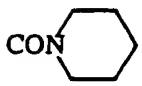

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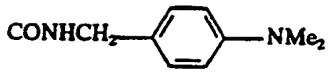

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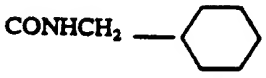

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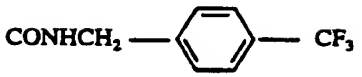

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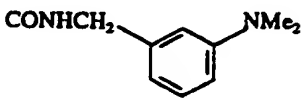

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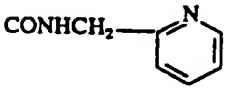

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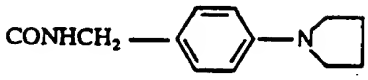
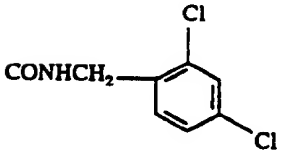


, CONHCH$_2$CF$_3$,



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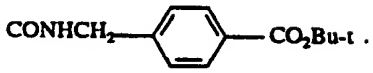

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It is to be understood that the present invention includes all combinations of the aforementioned particular and preferred groups.

Particularly preferred compounds according to the invention are [2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]]; [2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(2,2,2-trifluoroethyl)-2-thiazolidineacetamide]]; [2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(2-phenylethyl)-2-thiazolidineacetamide]]; [2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(3-methyl-1-oxobutyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]]; [2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-[(4-methoxyphenyl)methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]; [2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]; [2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-dimethyl-4-[[[[[[5,5-dimethyl-2-[2- oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-

thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-α-[(2-phenyl-1-oxoethyl)amino]-N-[(2-pyridinyl)methyl]-2-thiazolidineacetamide;

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-dimethyl-4-[[[[[[5,5-dimethyl-2-[2- oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-(phenylmethyl)-α-[[1-oxo-2-(2-pyridinyl)ethyl]amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5- dimethyl-α-[[[(1,1'-biphenyl)-2-yl]carbonyl]amino]-N-phenylmethyl-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-[(2,4-dichlorophenyl)methyl]-5,5-dimethyl-α-[(2-pyridinylacetyl)amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[[(4-dimethylamino)phenyl]methyl]-α[(phenylacetyl)amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[(N-methylamino) carbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-N-(phenylmethyl)-α-[[[(1,1'-biphenyl)-2-yl]carbonyl] amino]-2-thiazolidine acetamide]];

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-N-[(2,4-dichlorophenyl)methyl]-5,5-dimethyl-4-[[[[[[5,5,-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl] amino]carbonyl]-α-[[1-oxo-2-(2-pyridinyl)ethyl]amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-α-[[2-(4-chlorophenyl)-1-oxoethyl]amino]-5,5-dimethyl]-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[(2-pyridinyl)methyl]-2-thiazolidineacetamide;

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[[(2-phenylcyclopropyl)carbonyl]amino]-N-(phenylmethyl)-2-thiazolidineacetamide]] (Isomer B);

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[[(3-dimethylamino)phenyl]methyl]-α-[(phenylacetyl) amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[α-[[(3-chloro)phenylacetyl]amino]-N-ethyl-5,5-dimethyl-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[(4-(((1,1-dimethyl)ethoxy)carbonyl)phenyl)methyl]-α-[(2-phenyl-1-oxoethyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β(R*S*)],2'R-[2'α(R*),4'β]]-4,4'-[(1-methyl-1,2-ethanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl) amino]-N-(phenylmethyl)-2-thiazolidineacetamide];

[2R-[2α(R*),4β(R*)],2'R-[2'α(R*),4'β]]-4,4'-[(1-methyl-1,2-ethanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide];

[2R-[2α(R*),4β(R*,S*)],2'R-[2'α(R*),4'β]]-4,4'-[(1-hydroxymethyl-1,2-ethanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-[(4-(1-pyrrolidinyl)phenyl) methyl]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[[(4-dimethylamino)phenyl]methyl]-α-[[[(1,1'-biphenyl-2-yl]carbonyl]amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[[4-(dimethylamino)phenyl]methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N,N-dimethyl-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-1,2-[ethanediylbis[aminocarbonyl]bis[N-(cyclohexylmethyl)-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazoleacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-[(4-(trifluoromethyl) phenyl)methyl]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-N,N'-[1,2-ethanediylbis[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-(1-piperidinyl)ethyl]-4-thiazolidinecarboxamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(3-phenyl-1-oxopropyl)amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(phenoxyacetyl)amino]-2-thiazolidineacetamide]];

and physiologically acceptable salts and solvates thereof.

The compounds of the invention possess antiviral activity. In particular compounds of the invention are effective in inhibiting the replication of retroviruses, including human retroviruses such as human immunodeficiency viruses (HIV's), the causative agents of AIDS.

There is thus provided as a further aspect of the invention a compound of formula (I) or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent, in particular as an antiviral agent, for example in the treatment of retroviral infections.

In a further or alternative aspect there is provided a method for the treatment of a viral infection, in particular an infection caused by a retrovirus such as HIV, in a mammal including man comprising administering a therapeutically effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

There is also provided in a further or alternative aspect of the invention the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of a viral infection, for example in the treatment of a retroviral infection.

The compounds of the invention are also potentially useful in the treatment of AIDS related conditions such as AIDS-related complex (ARC), progressive

generalised lymphadenopathy (PGL), AIDS-related neurological conditions (such as dementia or tropical paraparesis), anti-HIV antibody positive and HIV-positive conditions, Kaposi's sarcoma and thrombocytopenia purpura.

The compounds of the invention are also useful in the prevention of progression to clinical illness of individuals who are anti-HIV antibody or HIV-antigen positive and in prophylaxis following exposure to HIV.

The compounds of formula (I) or the physiologically acceptable salts or solvates thereof may also be used for the prevention of viral contamination of physiological fluids such as blood or semen in vitro.

Compounds of formula (I) may also be useful as intermediates in the preparation of other compounds of the invention.

The protease inhibiting properties of the compounds of the present invention can be demonstrated in vitro by their ability to inhibit the hydrolysis of an appropriate peptide substrate by HIV protease according to methods generally known in the art.

The antiviral activity of compounds of the invention may be demonstrated in vitro by their effect on cells infected with HIV-RF according to the following procedures :-

(a) C8166 cells were infected with HIV-1 (strain RF) at a moi of 1×10^{-3} infectious units/cell. Aliquots of 10^5 cells were added to each well of 24-well plates containing serial dilutions of test compounds at final concentrations of 50 μg/ml to 0.05 μg/ml in RPMI 1640 growth medium. Untreated infected cells and untreated uninfected cells were also included as controls. The plates were incubated at 37^0C/5% carbon dioxide for 3-4 days in humidified containers. The cells were examined daily for evidence of HIV-1 induced syncytium formation. The syncytia were quantified by reference to the untreated infected controls and the dose of compound required to reduce the cytopathic effect by 50% (EC_{50}) was calculated.

(b) Virus injections were prepared according to the inhibition of syncytium formation assay hereinabove. Supernatant fluids cleaved by centrifugation were assayed for p24 antigen using an ELISA kit. The synthesis of p24 core antigen was

quantified by reference to the untreated infected controls and the dose of compound required to reduce the cytopathic effect by 50%. (EC_{50}) was calculated.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

It will be further appreciated that the amount of a compound of the invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general however a suitable dose will be in the range of from about 1 to about 750mg/kg of bodyweight per day, such as about 3 to about 120mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90mg/kg/day, most preferably in the range of 15 to 60mg/kg/day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

The compound is conveniently administered in unit dosage form; for example containing 10 to 1500mg, conveniently 20 to 1000mg, most conveniently 50 to 700mg of active ingredient per unit dosage form.

Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 1 to about 75μM, preferably about 2 to 50μM, most preferably about 3 to about 30μM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1 to about 100mg of the active ingredient. Desirable blood levels may be maintained by a continuous infusion to provide about 0.01 to about 5.0 mg/kg/hour or by intermittent infusions containing about 0.4 to about 15mg/kg of the active ingredient.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable derivative therefor together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution, a suspension or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as

suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), or preservatives.

The compounds according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active ingredient in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Pharmaceutical formulations suitable for rectal administration wherein the carrier is a solid are most preferably presented as unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art, and the suppositories may be conveniently formed by admixture of the active compound with the softened or melted carrier(s) followed by chilling and shaping in moulds.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intra-nasal administration the compounds of the invention may be used as a liquid spray or dispersible powder or in the form of drops.

Drops may be formulated with an aqueous or non-aqueous base also comprising one more more dispersing agents, solubilising agents or suspending agents. Liquid sprays are conveniently delivered from pressurised packs.

For administration by inhalation the compounds according to the invention are conveniently delivered from an insufflator, nebuliser or a pressurised pack or other convenient means of delivering an aerosol spray. Pressurised packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges or e.g. gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

When desired the above described formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical compositions according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

The compounds of the invention may also be used in combination with other therapeutic agents for example other antiinfective agents. In particular the compounds of the invention may be employed together with known antiviral agents.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a physiologically acceptable derivative thereof together with another therapeutically active agent, in particular an antiviral agent.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof comprise a further aspect of the invention.

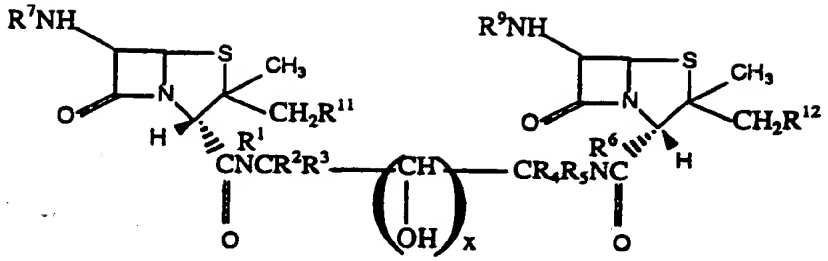
Suitable therapeutic agents for use in such combinations clude (-)-cis-4-amino-1-(2-hydroxymethyl-1,3-oxathiolane-5-yl)-(1H)-pyrimidin-2-one (3TC), 3'-azido-3'-deoxythymidine (AZT), ribavirin, 3'-azido-2',3'-dideoxyuridine, acyclic nucleosides such as acyclovir, interferons such as α-interferon, renal excretion inhibitors such as probenicid, inhibitors of retroviral protease, 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine 2',3'-dideoxyinosine and 2',3'-dideoxy-2',3'- didehydrothymidine, non-nucleoside reverse transcriptase (RT) inhibitors including TIBO compounds (e.g. Janssen's R82150), HEPT compounds and Boehringer Ingleheim's RG587, immunomodulators such as interleukin II (IL2) and granulocyte macrophage colony stimulating factor (GM-CSF), erythropoetin and ampligen.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same virus the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Suitable methods for preparing compounds of formula (I) and their physiologically acceptable salts and solvates are described below.

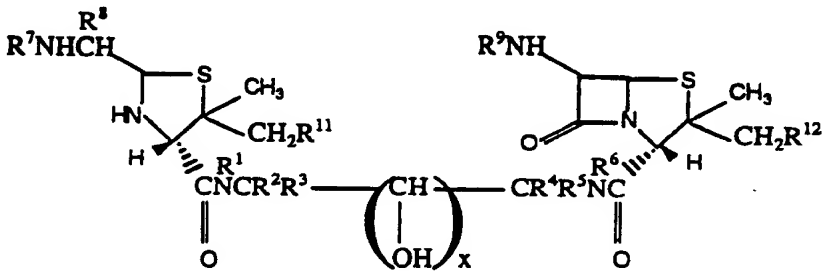
Thus, in a first process (A), compounds of formula (I) in which R^8 and R^{10} represent $COOR^{20}$ or $CONR^{21}R^{22}$ may be prepared from compounds of formula (II)



(II)

(wherein R^1-R^7, R^9. R^{11}, R^{12} and x are as defined previously) or protected derivatives thereof by treating said compounds of formula (II) with an appropriate nucleophile $R^{20}OH$ or $R^{21}R^{22}NH$, followed, where necessary, by the removal of any protecting groups present. When R^8 and R^{10} are different groupings the reaction with the compounds of formula (II) is effected in the presence of two different nucleophiles followed by separation of the desired product of formula (I). This process is particularly convenient however for preparing compounds of formula (I) in which R^8 and R^{10} are the same grouping.

In another process (B), compounds of formula (I) in which R^{10} represents $COOR^{20}$ or $CONR^{21}R^{22}$ may be prepared from compounds of formula (III)



(III)

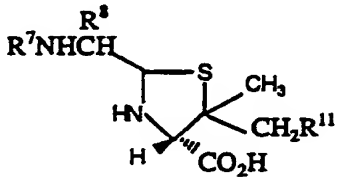
(wherein R^1-R^9, R^{11}, R^{12} and x are as defined previously) or protected derivatives thereof by treating said compounds of formula (III) with an appropriate nucleophile $R^{20}OH$ or $R^{21}R^{22}NH$, followed, where necessary, by the removal of any protecting groups present.

In each of processes (A) and (B) above the reaction is conveniently carried out in a suitable solvent such as water, a halogenated hydrocarbon (e.g. dichloromethane), an ether (e.g. tetrahydrofuran), an alcohol (e.g. ethanol or methanol) or a water-miscible solvent such as dimethylformamide or

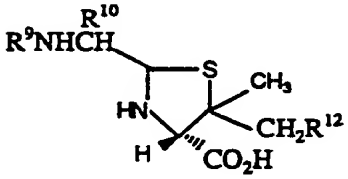
dimethylsulphoxide or a suitable mixture of such solvents at about room temperature. When R^{21} and R^{22} both represent hydrogen atoms the amination reaction is conveniently effected using aqueous ammonia solution. When R^{20} is C_{1-6}alkyl or ArC_{1-4}alkyl the reaction is effected using an alcohol $R^{20}OH$ or an alkali metal alkoxide (e.g. $NaOR^{20}$). When R^{20} is hydrogen the reaction is conveniently effected using a hydroxide such as sodium hydroxide.

In process (A) above, if appropriate, separation of the desired product of formula (I) may conveniently be carried out by chromatographic means (e.g. by column chromatography).

In a further process (C) compounds of formula (I) may be prepared by coupling the carboxylic acids of formulae (IV) and (V)



(IV)



(V)

(wherein R^7-R^{12} are as defined previously) or salts and/or protected derivatives thereof with a diamine of formula (VI)

(VI)

(wherein R^1-R^6 and x are as defined previously) or a protected derivative thereof, followed, where necessary by the removal of any protecting groups present. The coupling may conveniently be effected in the presence of a coupling agent such as 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate in the presence of a base such as N,N-diisopropylethylamine and in a suitable solvent (e.g. dimethylformamide) or N,N'-dicyclohexylcarbodiimide optionally in the presence of

1-hydroxybenzotriazole (or its hydrate) and in a suitable solvent such as a halogentated hydrocarbon (e.g. dichloromethane) or, more particularly, an ether (e.g. tetrahydrofuran). Under these conditions the reaction may conveniently be carried out at about room temperature. The coupling may alternatively be effected in the presence of ethyl chloroformate and N-ethylpiperidine in a suitable solvent such as a halogentated hydrocarbon (e.g. dichloromethane), conveniently at a temperature in the range of -20^0C to $+50^0C$.

When process (C) is carried out using two different acids of formulae (IV) and (V) the reaction may be effected by treating (VI) with the compounds of formulae (IV) and (V) followed by separation (e.g. using column chromatography) of the desired product of formula (I). However, the process preferably involves a first step of reacting a compound (IV) with a derivative of (VI) in which the $-NR^6H$ group is either protected or replaced by $-N_3$ followed by removal of the protecting group or reduction of the azide function to give a compound of formula (IX) hereinafter, and a second step of reacting said compound of formula (IX) with a compound of formula (V).

In another process (D) compounds of formula (I) may be converted to other compounds of formula (I).

In a particular embodiment of this process, compounds of formula (I) in which R^7 and/or R^9 represents an acylamino or sulphonylamino group may be prepared from the corresponding primary amine of formula (I) using conventional acylating or sulphonylating means. Thus, for example, a group CO_2CH_2Ar or CO_2CH_2Het may be introduced by reacting the amine with a haloformate (e.g. a chloroformate $ClCO_2CH_2Ar$ or $ClCO_2CH_2Het$) in a solvent such as water, preferably in the presence of a base such as an alkali metal carbonate (e.g. sodium carbonate). The amine may be regenerated from the so-formed grouping by treatment with an acid such as hydrobromic acid in acetic acid, conveniently in a solvent such as a halogenated hydrocabon (e.g. dichloromethane). A group COAr, COHet, $COCH_2R^{13}$, COCH=CHPh or COR^{14} may be introduced by reacting the amine with an appropriate acid in the presence of an activator such as 1-(3-

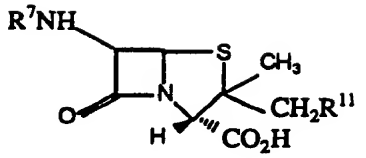
dimethylaminopropyl-3-ethylcardodiimide in a halogenated hydrocarbon solvent such as dichloromethane or in a solvent system comprising dioxane and water in the presence of triethylamine. Alternatively, the desired group may be introduced by reacting the amine with an anhydride in the presence of a suitable base such as an organic base (e.g. pyridine). A group SO_2Ar, SO_2Het, $SO_2CH_2R^{15}$, $SO_2CH{=}CHPh$ or SO_2R^{16} may be introduced by reacting the amine with an appropriate sulphonyl halide (e.g. a sulphonyl chloride) conveniently in a solvent such as a halaogenated hydrocarbon (e.g. dichloromethane) and preferable in the presence of a suitable base such as an organic base (e.g. triethylamine).

In another particular embodiment of process (D), compounds of formula (I) in which R^8 and/or R^{10} contains a carboxyl group may be prepared from the corresponding carboxylic acid ester of formula (I) using conventional means. Thus, for example, conversion of a t-butyl ester to be corresponding acid may conveniently be carried out by treating the ester with an acid such as hydrobromic acid in acetic acid, conveniently in a solvent such as a halogenated hydrocarbon (e.g. dichloromethane).

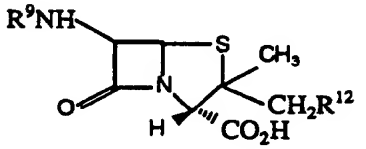
In a further embodiment of process (D), compounds of formula (I) in which R^{11} and/or R^{12} represents a hydroxyl group may be prepared from the corresponding compounds of formula (I) in which R^{11} and/or R^{12} represent an acetoxy group using conventional hydrolysis. Thus, for example, the hydrolysis may conveniently be carried out under basic conditions (e.g. using methanolic ammonia solution).

In another embodiment of process (D), compounds of formula (I) in which R^7 and/or R^9 represents $COCH_3$ may be prepared from the corresponding compounds of formula (I) in which R^7 and/or R^9 represents CO_2CH_2Ph. The conversation may conveniently be effected by treating the compound of formula (I) in which R^7 and/or R^9 represents CO_2CH_2Ph with acetic acid and hydrogen bromide in a suitable solvent such as a halogenated hydrocarbon (e.g. dichloromethane).

Compounds of formula (II) may be prepared by coupling the carboxylic acids of formulae (VII) and (VIII)



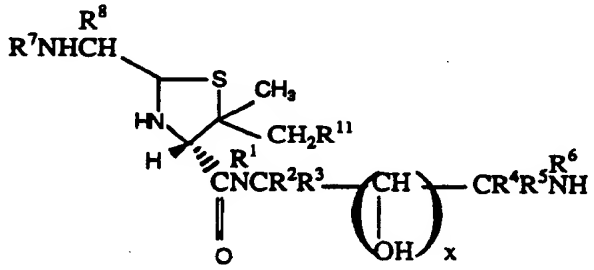
(VII)



(VIII)

(wherein R^7, R^9, R^{11} and R^{12} are as defined previously) or salts and/or protected derivatives thereof with a diamine of formula (VI) or a protected derivative thereof according to the procedure described in process (C) hereinabove, followed, where necessary, by the removal of any protecting groups present.

Compounds of formula (III) may conveniently be prepared by reacting a compound of formula (IX)



(IX)

(wherein R^1-R^8, R^{11} and x are as defined previously) or a protected derivative thereof with a compound of formula (VIII) or a protected derivative thereof under the conditions described for process (C) hereinabove, followed, where necessary, by the removal of any protecting groups present.

Compounds of formula (IX) may be prepared as described in process (C) hereinabove.

Compounds of formulae (IV) and (V) in which R^8 and R^{10} represent $COOR^{20}$ or $CONR^{21}R^{22}$ may be prepared by treating the corresponding compounds of formulae (VII) and (VIII) respectively with an appropriate nucleophile under the conditions described for process (A) or process (B) hereinabove. Compounds of formulae (IV) and (V) in which R^8 and/or R^{10}

represent C_{1-6}alkyl may be prepared from the corresponding compounds of formulae (IV) and (V) in which R^8 and/or R^{10} represent COOH using methodology well known to those of ordinary skill in the art.

Compounds of formulae (IV) and (V) in which R^8 and R^{10} are hydrogen and compounds of formulae (VI), (VII) and (VIII) are either known compounds or may be prepared from the known compounds of formulae (IV), (V), (VI), (VII) and (VIII) using conventional means.

It will be appreciated that some functional groups present in appropriate starting materials hereinabove may need to be protected, and deprotection may thus be required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be carried out using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g. benzyl), acyl or sulphonyl (e.g. allylsulphonyl or tosyl); subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in 'Protective Groups in Organic Chemistry', Ed. J. F. W. McOmie (Plenum Press, 1973) or 'Protective Groups in Organic Synthesis' by Theodora W. Greene (John Wiley and Sons, 1981). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g. methyl, t-butyl or methoxymethyl), aralkyl (e.g. benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydropyranyl, acyl (e.g. acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g. t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g. by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may similarly be removed by solvolysis, e.g. by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved by hydrogenolysis in the presence of a Noble metal catalyst such as palladium-on-charcoal. Silyl groups may also conveniently be removed using a source of fluoride ions such as tetra-n-butylammonium fluoride.

Carboxyl protecting groups may conveniently be protected using appropriate hydroxyl protecting groups above with deprotection effected according to the methods described above.

Particular isomers of formula (I) may either be prepared from starting materials having the desired stereochemistry or by epimerisation at an appropriate stage in the synthesis of the required compounds of formula (I). Epimerisation may be effected using conventional means, for example by treatment with an appropriate acid (e.g. according to the procedure described in Example 55 hereinafter).

It will be appreciated that interconversions as outlined in process (D) above may also be carried out on appropriate intermediates such that the desired R^7-R^{12} groupings are introduced prior to the final step conversion reaction.

Compounds of formulae (II), (III) and (IX) are novel intermediates and represent further aspects of this invention.

When it is desired to prepare an acid addition salt of a compound of formula (I) the product of any of the above procedures may be converted into a salt by treatment of the resulting free base with a suitable acid using conventional methods.

Physiologically acceptable acid addition salts of the compounds of formula (I) may be prepared by reacting a compound of formula (I) in the form of the free base with an appropriate acid optionally in the presence of a suitable solvent such as an ester (e.g. ethyl acetate) or an alcohol (e.g. methanol, ethanol or isopropanol).

Inorganic basic salts may be prepared by reacting the free base of a compound of formula (I) with a suitable base e.g. an alkoxide such as sodium methoxide optionally in the presence of a solvent (e.g. an alcohol such as methanol).

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of formula (I) using conventional methods.

Solvates (e.g. hydrates) of a compound of formula (I) may be formed during the work-up procedure of one of the aforementioned process steps.

The following Preparations and Examples illustrate the invention but do not limit the invention in any way. All temperatures are in ^0C.

Intermediate 1

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

Ethyl chloroformate (2.0ml) was added to a stirred solution of benzylpenicillin N-ethylpiperidine salt (9.0g) in anhydrous chloroform (120ml) at -11°. The solution was stirred at this temperature for 2h. Ethylenediamine (2.0ml) was added over 5 min keeping the temperature below 0° and a white precipitate was formed. The mixture was stirred for 2h with the temperature being allowed to gradually reach 19°. The mixture was filtered and the filtrate successively washed with 0.5N-hydrochloric acid, saturated aqueous sodium bicarbonate and 8%-aqueous sodium bicarbonate then dried and evaporated to a white foam (7.3g). This was crystallised from acetonitrile to afford the title compound as white prisms (3.89g), mp 195°. Concentration of the liquors provided a second crop of similar material (0.65g), mp 188°.

Intermediate 2

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-6-[(3-methyl-1-oxobutyl)amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

1,1,1,3,3,3-Hexamethyldisilazane (6.3ml) was added to a stirred suspension of 6-aminopenicillanic acid (5.0g) in dry chloroform (60ml). The mixture was heated under reflux for 2h and the solution cooled to 0-5°. A solution of isovaleryl chloride (2.1ml) in dichloromethane (20ml) was added dropwise and the solution stirred at 0-5° for 1.5h then evaporated in vacuo. The residue was treated with ethyl acetate to give a white solid which was removed by filtration. The filtrate was washed twice with water and with 0.5N-hydrochloric acid then dried and evaporated to give a white foam (4.3g). The bulk of this (4.2g) was dissolved in dry dichloromethane (60ml) and the solution treated with N-ethylpiperidine (1.86ml) and cooled to -10°. Ethyl chloroformate (1.33ml) was added and the solution stirred at -5° for 2h then ethylenediamine (1.4ml) was added. The mixture was stirred at +21° for a further

2h then filtered and the filtrate washed with 0.5N-hydrochloric acid, saturated sodium bicarbonate (twice) and water then dried and evaporated. The residue was subjected to chromatography on a column of silica gel (Merck Art 9385, 125g) using ethyl acetate-acetone (4:1 then 2:1) as eluant. Appropriate fractions were combined to give the title compound (1.20g), m.p. 236-237^0 (with decomposition), $[\alpha]_D$ +358^0 (c 1.0; $CHCl_3$).

Intermediate 3

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-7-oxo-6[[(phenylmethoxy)-carbonyl]amino]-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxamide]]

Benzyl chloroformate (6.6ml) was added to a stirred solution of 6-aminopenicillanic acid (10g) in water (250ml) containing sodium carbonate (5g). The mixture was stirred vigorously for 2.75h then washed with ethyl acetate. The aqueous portion was acidified to pH2 with stirring under a layer of ethyl acetate using concentrated hydrochloric acid. The layers were separated and the aqueous portion extracted with further ethyl acetate. The combined extracts were dried and evaporated to give a white foam (16.2g). This was dissolved in dry dichloromethane (250ml) and N-ethylpiperidine (6.2ml) added. The solution was cooled to -10^0 and ethyl chloroformate (4.4ml) added and the solution stirred at this temperature for 2h. Ethylenediamine (4.7ml) was added and the solution was allowed to warm to room temperature over 3h then successively washed with 0.5N-hydrochloric acid, brine solution and saturated aqueous sodium bicarbonate. The dried solution was evaporated to dryness and the residue chromatographed on silica gel (Fluka Kieselgel 60, 250g) eluting with ethyl acetate followed by ethyl acetate-acetone (4:1). Appropriate fractions were combined to give the title compound as a white solid (5.1g). A portion of this material was tritured with acetonitrile to give white crystals, mp 183^0.

Intermediate 4

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-ethyl-α-[[(phenylmethoxy)carbonyl]amino]-2-thiazolidineacetamide]]

A solution of ethylamine (0.45ml) in dichloromethane (4.05ml) was added to a solution of Intermediate 3 (950mg) in dichloromethane (5ml). The solution was stored for 20h then evaporated to dryness (1.02g). Crystallisation from ethyl acetate afforded the title compound as white prisms (930mg), $[\alpha]_D + 65^0$ (c 0.43, DMSO), ^1H nmr (DMSO-d_6) δ 0.99 (6H), 1.11 (6H), 1.46 (6H), 3.0-3.3 (8H), 3.41 (2H), 3.78 (2H), 4.01 (2H), 4.78 (2H), 5.03 (4H), 7.2-7.4 (12H) and 8.05 (

Intermediate 5

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[α-amino-5,5-dimethyl-N-ethyl-2-thiazolidineacetamide]]

A solution of 48% hydrobromic acid in acetic acid (12ml) in dichloromethane (100ml) was added to a stirred solution of the product of Intermediate 4 (2.0g) in dichloromethane (50ml). The mixture was stirred for 1h during which time a solid was precipitated. The supernatant was decanted and the solid washed by decantation using dichloromethane and then collected with the aid of ether to give the hydrobromide salt of the title compound (1.92g), m.p. 185-188^0 (with decomposition and prior softening). This material was dissolved in water (10ml), layered with ethyl acetate and basified with stirring using saturated sodium bicarbonate solution. The aqueous phase was saturated with ammonium sulphate and the layers separated. The aqueous portion was further extracted with chloroform (four times) and the combined organic portions were dried and evaporated. The residue was treated with ethyl acetate and filtered to give the title compound as a white solid (830mg), $[\alpha]_D + 94.8^0$ (c 0.75; Me_2SO).

Intermediate 6

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-6-[((5-methyl-3-phenyl-4-isoxazolyl)carbonyl)amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

A solution of oxacillin sodium salt (1.0g) in water was acidified in 2N-hydrochloric acid in the presence of ethyl acetate. The layers were separated and the aqueous portion extracted a further two times with ethyl acetate. The combined extracts were dried and evaporated to give a white foam. This was dissolved in dry dichloromethane (100ml) and cooled to -10^0. N-Ethylpiperidine (0.37ml) and ethyl chloroformate (0.23ml) were added and the mixture stirred at -10^0 for 0.5h. Ethylenediamine (0.24ml) was added and the mixture stirred for 2.5h at $+21^0$ then filtered. The filtrate was washed with 0.5N-hydrochloric acid and saturated sodium bicarbonate then dried and evaporated to give a foam. This was purified by chromatography on a column of silica gel (Merck Art 9385, 50g) using ethyl acetate as eluant to give a solid which was treated with ether to give the title compound as a white solid (480mg), m.p. 153^0 (with decomposition), $[\alpha]_D$ $+231^0$ (c 0.61; Me_2SO).

Intermediate 7

[2R-[2α(R*),4β]]-2-[2-(Ethylamino)-2-oxo-1-[(phenoxyacetyl)amino]ethyl]-5,5-dimethyl-4-thiazolidinecarboxylic acid

Ethylamine (2ml) was added to a stirred solution of phenoxymethylpenicillin (1.0g) in dichloromethane-ether (1:1; 100ml). The mixture was allowed to stand overnight then evaporated to a cream solid (1.15g). The bulk of this material (1.0g) was dissolved in water and the pH adjusted to 2.0 with orthophosphoric acid. The acidified solution was extracted with ether and ethyl acetate and the combined extracts were dried and evaporated to give the title compound as a white solid (0.80g), $[\alpha]_D$ + 59° (c 0.55; MeOH).

Intermediate 8

[2R-[2α(R*),4β]]-4,4'-1,2-[Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[[(phenylmethoxy)carbonyl]amino]-N-(phenylmethyl)-2-thiazolidineacetamide]]

Benzylamine (1.2ml) was added to a stirred solution of Intermediate 3 (1.3g) in dichloromethane (50ml) and the solution left for 3 days. The solution was successively washed with 0.5N-hydrochloric acid, saturated aqueous sodium

bicarbonate and brine solution then dried and evaporated to give a white solid which crystallised from acetonitrile to afford the title compound as white prisms (341mg), mp 115^0, $[\alpha]_D + 25^0$ (c 1.1, MeOH).

Intermediate 9

[2R-[2α(R*),4β]]-4,4'-1,2-[Ethanediylbis[aminocarbonyl]bis[α-amino-5,5-dimethyl-N-(phenylmethyl)-2-thiazolidineacetamide]]

A 45%-solution of hydrobromic acid in acetic acid (10ml) was added to a stirred solution of Intermediate 8 (684mg) in dichloromethane (300ml). The mixture was stirred for 1.50h then extracted with water (300ml) and 0.5N-hydrochloric acid (160ml). The combined aqueous extracts were basified and extracted with dichloromethane. The dried organic solution was evaporated to give an off-white solid (405mg) which crystallised from acetonitrile to afford the title compound as white prisms (114mg), mp 179-180^0, $[\alpha]_D + 22.5^0$ (c 1.0, MeOH).

Intermediate 10

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[[(phenylmethoxy)carbonyl]amino]-N-[2-(pyridinylmethyl)]-2-thiazolidineacetamide]]

2-Aminomethylpyridine (4.8ml) was added to a solution of Intermediate 3 (8.4g) in dichloromethane (250ml). The solution was stirred at +21° for 21h during which time precipitation occurred. The solid was collected by filtration, washed with dichloromethane and ether and dried to give the title compound as a white solid (6.58g). A portion of this material was crystallised from acetonitrile to afford white prisms, m.p. 160 - 161°, $[\alpha]_D + 44°$ (c 1.0; MeOH).

Intermediate 11

[2R-[2α(R*),4β]]-4,4-[1,2-Ethanediylbis[aminocarbonyl]bis[α-amino-5,5-dimethyl-N-(2-pyridinylmethyl)-2-thiazolidineacetamide]]

A 30% solution of hydrogen bromide in acetic acid (20ml) was added slowly with stirring to a solution of the product of Intermediate 10 (2.0g) in acetonitrile (200ml). The mixture was stirred for 45 min and the precipitated solid collected by filtration, washed with dichloromethane and ether and dried (1.5g). A portion of this (0.93g) was dissolved in water and neutralized with sodium bicarbonate. The solution was saturated with ammonium sulphate and extracted with dichloromethane several times. The combined extracts were dried and evaporated to give the title compound as a white solid (515mg), ^{1}H nmr (DMSO-d_6) δ 1.17(6H), 1.48(6H), 2.23(4H), 2.9-3.3(4H), 3.96(2H), 4.37(6H), 4.68(2H), 7.2-7.4(4H), 7.74(2H), 8.06(2H), 8.49(2H) and 8.59(2H).

Intermediate 12

[2R-[2α(R*),4β]]-4,4-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[(4-chlorophenyl)methyl]-5,5-dimethyl-α-[((phenylmethoxy)carbonyl) amino]-2-thiazolidineacetamide]]

4-Chlorobenzylamine (0.68ml) was added to a stirred solution of Intermediate 3 (1.0g) in dry dichloromethane (30ml). The solution was stirred for 22h and additional 4 - chlorobenzylamine (0.68ml) was added. Stirring was continued for a further 19h, then the reaction solution was washed with 0.5N - hydrochloric acid, saturated sodium bicarbonate solution and brine, then dried and evaporated (1.01g). This was purified by column chromatography on silica gel (Merck Art 9385, 100g) using ethyl acetate to give the title compound as a white solid (337mg). A small portion was crystallised from acetonitrile to afford white prisms, mp. 155-158°, $[\alpha]_D$ + 37° (c 1.03; MeOH).

Intermediate 13

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[α-amino-N-[(4-chlorophenyl)methyl]-5,5-dimethyl-2-thiazolidineacetamide]]

30% Hydrogen bromide in acetic acid (2ml) was added to a stirred suspension of Intermediate 12 (408mg) in dichloromethane (20ml). The resulting solution was

stirred for 45 min during which time a solid was deposited. This was collected, washed with dichloromethane and ether and dried (388mg). The solid was dissolved in water (20ml) and the pH adjusted to 8.0 with sodium bicarbonate solution. The aqueous solution was saturated with ammonium sulphate and extracted in turn with chloroform, ethyl acetate and chloroform-methanol. The combined extracts were dried and evaporated to give the title compound (244mg) as a white foam, ^{1}H nmr (DMSO-d_6) δ 1.14(6H), 1.46(6H), 2.00(2H), 3.17(8H), 3.92(2H), 4.23(4H), 4.61(2H), 7.31(8H), 8.02(2H), and 8.45(2H).

Intermediate 14

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[(2,4-dichlorophenyl)methyl]-5,5-dimethyl-α-[[(phenylmethoxy)carbonyl] amino]-2-thiazolidineacetamide]]

2,4-Dichlorobenzylamine (3.75ml) was added to a stirred solution of Intermediate 3 (2.50g) in dichloromethane (50ml) under an atmosphere of nitrogen. The solution was stirred for 3.5 days, then washed with water, 0.5N - hydrochloric acid, saturated sodium bicarbonate solution and brine. The solution was dried and evaporated to give a pale yellow solid (3.265g) which was chromatographed on a column of silica gel (Merck Art 9385, 200g) using ethyl acetate followed by ethyl acetate - acetone (9:1). Appropriate fractions were combined to give the title compound as a white solid (1.73g). A portion of this material was crystallised from acetonitrile to afford white prisms, m.p. 145-147°; $[a]_D$ + 26° (c 1.0; MeOH).

Intermediate 15

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[α-amino-N-[(2,4-dichlorophenyl)methyl]-5,5-dimethyl-2-thiazolidineacetamide]]

30% - Hydrogen bromide in acetic acid (7ml) was added to a stirred solution of Intermediate 14 (1.47g) in dichloromethane (70ml). The solution was stirred for 45 min during which time a solid precipitated. This was collected, washed with dichloromethane and ether and dried (1.51g). The pale orange solid was dissolved

in water (100ml) and the pH taken to 8 with saturated sodium bicarbonate solution. The solution was saturated with ammonium sulphate and extracted several times with chloroform. The organic extracts were dried and evaporated to give the title compound as an off-white foam (230mg), ^{1}H nmr (DMSO-d_6) δ 1.15(6H), 1.47(6H), 1.90(4H), 3.20(6H), 3.41(2H), 3.95(2H), 4.29(4H), 4.63(2H), 7.39(4H), 7.57(2H), 8.05(2H) and 8.52(2H).

Intermediate 16

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-N-methyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]].

A stirred solution of benzylpenicillin potassium salt (50g) in water (400ml) under a layer of ethyl acetate (400ml) was adjusted to pH3 with orthophosphoric acid. The organic phase was separated, washed with water and brine, then dried and evaporated to an off-white foam (45.1g). A portion of this (5.15g) was dissolved in dichloromethane (100ml) and N, N' - dicyclohexylcarbodiimide (3.175g) and N, N' - dimethylethylenediamine (0.82ml) were added. The resulting suspension was stirred at +21° for 16h under an atmosphere of nitrogen then filtered. The filtrate was evaporated and the bulk (3.20g) of the residue (4.20g) was chromatographed on a column of silica gel (Merck Art 9385, 150g) using ethyl acetate-acetone (2:1). Appropriate fractions were combined to give the title compound as an off-white foam (688mg), ^{1}H nmr (DMSO-d_6) (mixture of rotamers) δ 1.38 and 1.36(6H), 1.58 and 1.63(6H), 3.04(4H), 3.30(6H), 3.52(4H), 3.58(1H), 3.82(1H), 4.78(1H), 4.92(1H), 5.28(1H), 5.38(1H), 5.47(2H), 7.24(10H), and 8.72(2H).

Intermediate 17

[2R-[2α(R*),4β]]-4-[[(2-Aminoethyl)amino]carbonyl]-5,5-dimethyl-α-[(phenylacetyl)amino-N-(phenylmethyl)-2-thiazolidineacetamide.

Ethyl chloroformate (0.95ml) was added to a stirred solution of benzylpenicillin N-ethylpiperidine salt (4.5g) in anhydrous dichloromethane (100ml) at -10° under an atmosphere of nitrogen. The solution was stirred at -10° for 2h and

then sequentially washed with cold 0.2M-sodium phosphate buffer (pH7) and saturated brine solution. A solution of 2-azidoethylamine (1.22g) in 4N-sodium hydroxide (2.5ml) was added followed by cetyltrimethylammonium bromide (350mg). The solution was stirred at 21° for 75 min and then sequentially washed with water, saturated sodium bicarbonate, brine solution, water, 0.5N-hydrochloric acid, water and saturated brine. The dried solution was evaporated to give a white foam (3.55g). A portion (2.0g) of this material was dissolved in anhydrous dichloromethane (100ml) and benzylamine (2.7ml) added. The solution was stirred for 70h then treated with 0.5N-hydrochloric acid to give a white precipitate which was collected by filtration. The solid was partitioned between dichloromethane and saturated sodium bicarbonate and the organic layer dried and evaporated to give a white foam (1.92g). This was further purified by column chromatography on silica gel (Merck Art 9385) using ethyl acetate-ether (4:1) to give a white foam (1.23g). The bulk of this (1.08g) was dissolved in ethanol (125ml) and 10%-palladium on charcoal (0.94) was added. The mixture was stirred under an atmosphere of hydrogen for 1.5h then filtered and evaporated to dryness. The residue was treated with acetone and re-evaporated to give the title compound as an off-white foam (0.85g), $[\alpha]_D + 56°$ (c 0.5; Me_2SO).

Intermediate 18

[2S-[2α,5α,6β]]-3,3-Dimethyl-7-oxo-6-[[phenylmethoxy)carbonyl] amino}-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

Sodium carbonate (0.28g) was added to a stirred suspension of 6-aminopenicillanic acid (0.55g) in water (17ml) to give a clear solution. Benzyl chloroformate (0.36ml) was added and the mixture was stirred vigorously for 4h then washed with ethyl acetate. The aqueous portion was then stirred with ethyl acetate and the pH adjusted to 2.0 with orthophosphoric acid. The organic layer was separated and the aqueous portion extracted with further ethyl acetate. The combined organic portions were dried and evaporated to give the title compound as

a white foam (0.85g), ^{1}H nmr (DMSO-d_6) δ 1.47(3H), 1.59(3H), 4.22(1H), 5.07(2H), 5.37(1H), 5.47(1H), 7.23-7.44(5H) and 8.26(1H).

Intermediate 19

[2S-[2α,5α,6β]2'R-[2'α(R*),4'β]]-3,3-Dimethyl-2-[[[[5,5-dimethyl- 2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]-7-oxo-6-[[(phenylmethoxy) carbonyl]amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide.

N-Hydroxybenzotriazole (0.34g) was added to a stirred solution of Intermediate 17 (0.82g) and Intermediate 18 (0.71g). N,N-Dicyclohexycarbodiimide (0,46g) was added and the mixture stirred for 4h then filtered. The filtrate was evaporated and the residue treated with ethyl acetate and again filtered. The organic phase was washed with sodium bicarbonate solution and saturated brine, then dried and evaporated to give the title compound as a brown foam (1.45g), $[\alpha]_D + 74^0$ (c 0.50; Me_2SO).

Intermediate 20

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-N-[(2,4- Dichlorophenyl)methyl]- 5,5-dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-α-[[(phenylmethoxy)carbonyl]amino]-2-thiazolidineacetamide.

2,4-Dichlorobenzylamine (0.57ml) was added to a stirred solution of Intermediate 19 (1.43g) in anhydrous dichloromethane (35ml) under an atmosphere of nitrogen. The solution was stirred for 2 days then filtered to remove a small amount of solid. The filtrate was washed with 0.5N-hydrochloric acid and brine solution then evaporated to give a brown solid (1.39g). This was purified on a column of silica gel (Merck Art 9385) using dichloromethane-methanol (15:1) to give a white solid (1.39g). A portion of this material was crystallised from ethyl

acetate to provide the title compound as white prisms (110mg), mp 135-138°, $[\alpha]_D$ + 57° (c, 1.60; Me_2SO).

Intermediate 21

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-7-oxo-6-triphenylmethylamino)-4-thia-1-azabicyclo{3.2.0}heptane-2-carboxamide]]

1-Hydroxybenzotriazole hydrate (17.7g), ethylenediamine (3.7ml) and N,N-dicyclohexylcarbodiimide (25.9g) were added in turn to a stirred solution of N-trityl 6-aminopenicillanic acid (50.0g) in ethyl acetate (300ml). The mixture was stirred for 17h then glacial acetic acid (ca 5ml) was added dropwise. The suspension was cooled to ca 5° and filtered. The filtrate was sequentially washed with 2N-hydrochloric acid, water, saturated sodium bicarbonate, water and brine then dried and evaporated to give a yellow foam (55g). This was purified on a column of silica gel (Merck Art 9385, 650g) using ethyl acetate-cyclohexane (2:1) to give the title compound as an off-white solid (39.7g), $[\alpha]_D$ + 96° (c 0.94, MeOH).

Intermediate 22

[2S-[2α,5α,6β]-N,N'-[1,2-Ethanediylbis[6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]], 4-methylbenzenesulphonic acid salt

Toluenesulphonic acid (24.0g) was added to stirred solution of Intermediate 21 (60.65g) in acetone (600ml). The mixture was stirred for 3.5h during which a solid was precipitated. This was collected, washed with ether to give the title compound as a pale yellow solid (41.2g), $[\alpha]_D$ + 135° (c 1.07, MeOH).

Intemediate 23

[2S-[2α,5α,6β]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-7-oxo-6-[[(2-phenylcyclopropyl)carbonyl]amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]].

A stirred mixture of Intermediate 22 (7.0g) in water (60ml)-ether (50ml) was adjusted to pH by the addition of solid sodium hydrogen carbonate. The layers were

separated and the aqueous portion washed with ethyl acetate (50ml), saturated with ammonium sulphate and extracted with chloroform - ethanol (19:1). The extract was dried and evaporated to give a pale yellow solid (2.4g). A portion of this material (658mg) was suspended in water (20ml) and treated with a solution of cis-2-phenyl-1-cyclopropanecarboxylic acid (514mg) in dioxan (20ml) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (662mg). The resulting solution was stirred for 2h then diluted with ethyl acetate and washed with saturated sodium bicarbonate and brine. The dried solution was evaporated to give the title compound as a light yellow powder (1.15g), ^{1}H nmr ($CDCl_3$) δ 1.1-1.4, 1.7-2.0 and 2.3-2.7(8H), 1.43(6H), 1.68(6H), 3.30(4H), 4.08(2H), 5.13 and 5.24(2H), 5.50(2H), 6.22(2H), 7.05(2H) and 7.15-7.35(10H).

Intermediate 24

[2S-[2α,5α,6β]2'R-[2'α(R*)4β]]-3,3-Dimethyl-2-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide

N,N'-Dicydohexylcarbodiimide (3.80g) was added to a solution of penicillin G (5.66g), Intermediate 17 (6.79g) and 1-hydroxybenzotriazole (2.85g) in tetrahydrofuran (500ml). The reaction was stirred for 5h during which time a solid precipitated. The suspension was filtered and the filtrate evaporated to a solid. This was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution and brine then dried and evaporated. The residue was purified by column chromatography on silica gel (Merck Art 9385, 300g) using ethyl acetate-acetone (3:1) to afford the title compound (5.45g), $[\alpha]_D + 67^0$ (c 0.6; Me_2SO).

Intermediate 25

[2S-[2α,5α,6β]]-N,N'-[1,2,-Ethanediylbis[3,3-dimethyl-7-oxo-6-[((2Z)-3-phenyl-1-oxo-2-propenyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

A solution of cis-cinnamic acid (347mg) in dioxan (15ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (430mg) was added to a stirred solution of Intermediate 22 free base (500mg) (as prepared in Intermediate 32). The mixture was stirred for 8h, then further 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100mg) was added. The mixture was stirred for 16h, then extracted with ethyl acetate. The separated organic phase was washed with water, sodium bicarbonate solution and brine then dried and evaporated. The solid was purified by column chromatography on silica gel (Merck Art 9385, 25g) using acetone:cyclohexane (1:1) to afford the title compound as a white solid (160mg), IR νmax (NUJOL) 1786, 1659 and 1524cm^{-1}.

Intermediate 26

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[6-[((2-hydroxy)phenylacetyl) amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

A stirred solution of Intermediate 22 (6.0g) in water (60ml)and ethyl acetate (40ml) was basified to pH8 with sodium bicarbonate. The layers were separated and ammonium sulphate was added to the aqueous phase. The near saturated solution was extracted with 5% ethanol in chloroform and the organic layer was dried and evaporated to give an off white solid (1.2g). 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (600mg) and 2-hydroxyphenylacetic acid (500mg) were added to a stirred solution of a portion of this solid (350mg) in water (15ml) and dioxan (15ml). The solution was stirred for 72h and more of the carbodiimide (135mg) and the acid (120mg) were added. Stirring was resumed for 24h, after which a further portion of the carbodiimide (110mg) was added. Stirring was resumed for 3h and more of the acid (50mg) and the carbodiimide (50mg) were added. The solution was stirred for another hour and then extracted with ethyl acetate. The organic layer was washed sequentially with water, saturated sodium bicarbonate solution and brine, dried and evaporated to yellow brown gum. This was triturated with ether to afford the title compound as an off white solid (220mg), mp 149-151°, $[\alpha]_D$ +231° (c 0.41, MeOH).

Intermediate 27

[2R-[2α(R*),4β]]-2-[2-(Ethylamino)-2-oxo-1-[(phenylacetyl) amino]ethyl]-5,5-dimethyl-4-thiazolidinecarboxylic acid

Anhydrous ethylamine (4ml) was added slowly to an ice-cold solution of benzylpenicillin N-ethylpiperidine salt (6.5g) in dichloromethane (150ml). The solution was stirred at 21° for 15h. The resulting suspension was cooled and the solid was filtered off and washed with dichloromethane (30ml). The solid was suspended in a stirred mixture of water (50ml) and dichloromethane (50ml) and orthophosphoric acid was added to pH3. The organic phase was separated and the aqueous phase was extracted with dichloromethane (50ml). The combined organic phases were washed sequentially with water and saturated brine to give the title compound (2.375g) as a solid, $[\alpha]_D$ 21° +90° (c 0.84, MeOH).

Intermediate 28

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-7-oxo-6-[(((2-phenylmethyl)phenyl)carbonyl)amino]-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxamide]]

A solution of Intermediate 22 (2g) in aqueous sodium bicarbonate solution (20ml) was washed with ethyl acetate. The aqueous phase was saturated with ammonium sulphate and was extracted with chloroform-ethanol (19:1). The organic extracts were dried and evaporated. The residue was suspended in dichloromethane (100ml) and α-phenyl-2-toluic acid (0.93g) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.84g) were added. The mixture was stirred at +21° for 20h then washed sequentially with water, aqueous sodium bicarbonate solution and brine. The organic solution was dried and evaporated. The residue was chromatographed on a column of silica gel (Merck Art 9385; 50g) using ethyl acetate. Appropriate fractions were combined and evaporated. Trituration of the residue with ether gave the title compound as a solid (0.355g), $[\alpha]_D$ +266° (c 0.8, Me_2SO).

Intermediate 29

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[(4-(((1,1-dimethyl)ethoxy)carbonyl)phenyl)methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

4-(Aminomethyl) benzoic acid 1,1-dimethylethyl ester acetic acid salt (1.82g) was added to a stirred solution of Intermediate 1 (1.00g) in dichloromethane (40ml). The reaction solution was stirred for 72h, then triethylamine (1.22ml) and additional amine acetic acid salt (0.52g) were added. Stirring was resumed for 24h, after which the solution was washed sequentially with water, 0.5N hydrochloric acid, water, saturated sodium bicarbonate solution, water and brine, dried and evaporated to give the title compound as a pale yellow solid (1.51g). Crystallisation from acetonitrile afforded white prisms (750mg), mp 149-150°, $[\alpha]_D$ +8.9° (c 0.51, MeOH).

Intermediate 30

[2S-[2α,5α,6β],2'S-[2'α,5'α,6'β(R*,S*)]]-N.N'-[1-methyl-1,2- ethanediylbis[3,3-dimethyl-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

Ethyl chloroformate (1.1ml) was added to a stirred, cooled (-10°) solution of penicillin G N-ethylpiperidine salt (5g) in dichloromethane (70ml) under nitrogen. After 2.5h the solution was washed with pH7 phosphate buffer and brine. The dried solution was divided into two equal portions, one of which was treated with 1,2-diaminopropane at -10°. The reaction was stirred at 20° for 3h and then washed sequentially with 0.5N-hydrochloric acid, water, saturated sodium bicarbonate, water and brine. The dried solution was evaporated to a white foam which was purified by silica-gel chromatography (Merck 9385, 40g) eluting with chloroform : methanol mixtures 20:1 and 15:1. The white foam obtained was triturated with diethyl ether to give a white powder, MS (CI) $^{m}/_{e}$ 707 (MH^+) ^{1}H nmr ($CDCl_3$) δ 1.10 - 1.20 (3H), 1.45 (6H), 1.63 (6H), 3.10 - 3.40 (2H), 3.61 (2H), 3.90 - 4.05 (1H),

4.09 (2H), 5.30 - 5.41 (2H), 5.68 - 5.78 (2H), 6.07 - 6.16 (2H), 6.88 (1H), 6.92 - 7.15 (1H) and 7.22 - 7.42 (10H).

Intermediate 31

(R,S)-2,3-Diaminopropane-1-ol, dihydrochloride salt

A solution of di-t-butyl dicarbonate (17.0g) in dioxan (100ml) was added to a solution of (R,S)-2,3-diaminopropionic acid monohydrochloride (5.0g) in 2N-sodium hydroxide (100ml). The solution was stirred for 3h then partioned between ethyl acetate and water. The aqueous portion was acidified to pH3 with 2N-hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with brine then dried and evaporated to a colourless gum, which crystallised from ether to give white crystals (6.38g), mp 163-164°.

A portion of this material (1.00g) was dissolved in N,N-dimethylformamide (10ml) and the solution treated with potassium carbonate (0.67g) and methyl iodide (0.44ml). The solution was stirred for 1h then partitioned between ethyl acetate and water. The organic portion was washed with water, aqueous sodium bicarbonate and brine, then dried and evaporated to an oil. This was crystallised from cyclohexane to give white crystals (0.87g), mp 111-112°.

The bulk of this material (640mg) was dissolved in dry tetrahydrofuran (5ml) at 0° under nitrogen and 1M-lithium aluminium hydride in tetrahydrofuran (1.8ml) was added. The solution was stirred at this temperature for 1h and water (0.06ml), 2N-sodium hydroxide (0.12ml) and water (0.12ml) were added. The mixture was stirred at +21° for 10 min then filtered and the filtrate partitioned between ethyl acetate and water. The organic portion was washed with brine, dried and evaporated to give a white solid, crystallisation from cyclohexane afforded white crystals (360mg), mp 105-106°.

The major part of this material (347g) was dissolved in 2M-hydrogen chloride in methanol (10ml). The solution was stirred with 4h then evaporated to give the title compound as a white solid (190mg), mp >150°, ^{1}H nmr (DMSO-d_6) δ 3.08 (2H), 4.43 (1H), 3.62 (2H), 5.52 (1H) and 8.46 (6H).

Intermediate 32

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-6-[((3-methyl)phenylacetyl)amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

Intermediate 22 (7.11g) was added to water (50ml) and ethyl acetate (50ml) and then basified by the addition of saturated sodium bicarbonate solution. The aqueous phase was separated and then almost saturated with ammonium sulphate. The solution was extracted three times with chloroform-ethanol (95:5). The combined organic extracts were dried and evaporated to afford Intermediate 22 free base (4.8g) as a foam.

A solution of m-tolylacetic acid (351mg) in dioxan (15ml) and 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (351mg) was added to a stirred solution of the above free base (500mg) in water (15ml). The mixture was stirred for 8.5h, then further 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100mg) was added. Stirring was continued for a further 16h then the suspension was filtered. The collected solid was washed with water and dried, to afford the title compound as a white solid (558mg), $[\alpha]_D$ +317° (c 0.5, Me_2SO).

Intermediate 33

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-7-oxo-4-thia-6-[(2-thienylacetyl)amino]-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

A solution of 2-thiopheneacetic acid (0.33g) in dioxan (15ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (430mg) were added to a stirred solution of Intermediate 22 free base (500mg) (as prepared in Intermediate 32) in water (15ml). The mixture was stirred for 20h, then extracted with ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate solution and brine then dried and evaporated to afford the title compound as a white solid (690mg), $[\alpha]_D$ +294° (c 0.6, Me_2SO).

Intermediate 34

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[6-[((3-chloro)phenylacetyl) amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

A solution of m-chlorophenylacetic acid (399mg) in dioxan (15ml) and 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (351mg) were added to a stirred solution of Intermediate 22 free base (500mg) (as prepared in Intermediate 32). Stirring was continued for 20h, then the suspension was filtered. The collected solid was washed with water and dried to afford the title compound as a white solid (280mg), $[\alpha]_D$ +304° (c 0.5, Me_2SO).

Intermediate 35

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[3,3-dimethyl-7-oxo-4-thia-6-[(3-thienylacetyl)amino]-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

A solution of 3-thiopheneacetic acid (330mg) in dioxan (15ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (430mg) were added to a stirred solution of Intermediate 22 free base (as prepared in Intermediate 32). The mixture was stirred for 8h then additional 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100mg) was added. The mixture was stirred for 10h then extracted with ethylacetate. The separated organic phase was washed with water, saturated sodium bicarbonate solution and brine then dried and evaporated to give the title compound as an off white solid (717mg), $[\alpha]_D$ +287° (c 0.70, Me_2SO).

Intermediate 36

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[6-[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl)carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

A stirred solution of cloxacillin sodium salt (2g) in water (30ml) under a layer of ethyl acetate was adjusted to pH2 with 2N-hydrochloric acid. The layers were separated and the aqueous portion was extracted twice with ethyl acetate. The

combined extracts were dried and evaporated to give a white foam (ca 2g). This was dissolved in dry dichloromethane (150ml) and cooled to -10° under an atmosphere of nitrogen. N-Ethylpiperidine (0.69ml) and ethyl chloroformate (0.42ml) were added and the solution stirred at -10° for 30 min. Ethylenediamine (0.44ml) was added dropwise and the mixture was allowed to warm to room temperature over 2.5h. The mixture was filtered and the filtrate washed with 0.5N-hydrochloric acid, saturated brine and sodium bicarbonate solution, then dried and evaporated to give the title compound as a white foam (1.61g), $[\alpha]_D$ + 167^0 (c 1.1; Me_2SO).

Intermediate 37

(R,S)-2,3-Diaminopropanoic acid, phenylmethyl ester, dihydrochloride

Potassium carbonate (0.81g) and benzyl bromide (0.38ml) were added to a solution of (R,S)-N,N'-(1-carboxy-1,2-ethanediyl)bis(carbamic acid,1,1-dimethylethyl ester) (1.00g) (prepared as in Intermediate 31) in dry N,N-dimethylformamide (10ml). The mixture was stirred under nitrogen for 1h then partitioned between ether and water. The organic phase was washed with brine then dried and evaporated to give a white solid which crystallised from cyclohexane to give white prisms (1.20g).

The bulk of this material (1.10g) was dissolved in 2M-methanolic hydrogen chloride (10ml)-chloroform (10ml) and the solution stirred for 3h then evaporated to give the title compound as a white solid (0.70g), mp 168° (dec), ^{1}H nmr (DMSO-d_6) δ 3.22 (2H), 4.36 (1H), 5.14 (2H), 7.32 (5H) and 8.80 (6H).

Intermediate 38

[2R-[2α(R*),4β(R*,S*)],2'R-[2'α(R*),4'β]]-4,4'- [((1-(Phenylmethoxy)carbonyl)-1,2-ethanediyl)bis(aminocarbonyl)]bis-[5,5-dimethyl-α-[(phenylacetyl)amino-N-(phenylmethyl)-2-thiazolidineacetamide]

To a solution of [2R-(2α(R*),4β]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidine carboxylic acid (661mg), Intermediate 37 (200mg) and 2-(1H benzotriazol-1-yl)-1,1,3,3-

tetramethyluronium tetrafluoroborate (488mg) in N,N-dimethylformamide (10ml) was added N,N-diisopropylethylamine (521μl) and the resulting solution stirred at 21° under nitrogen for 18h. The reaction was partitioned between ethyl acetate and 10% aqueous citric acid. The organic phase was washed with saturated aqueous sodium hydrogen carbonate, water and brine then dried and evaporated. The residual solid was purified by chromatography on silica gel (Merck 7734, 60g) eluting with ethylacetate-cyclohexane (1:1 to 1:0) to give a colourless gum which crystallised from ether to give the title compound as white prisms (263mg), mp 135-138°, $[\alpha]_D$ +60° (c 0.93, $CHCl_3$).

Intermediate 39

[2S-[2α,5α,6β]]-6-[[[(1,1'-Biphenyl)-2-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

A mixture of 2-phenylbenzoic acid (20g) and thionyl chloride (50ml) was heated under reflux for 2h then excess thionyl chloride was removed by distillation. The residue was treated with toluene and re-evaported. The resulting acid chloride was dissolved in acetone (50ml) and the solution was added dropwise to a stirred solution of 6-aminopenicillanic acid (25g) in acetone-water (2:1, 300ml) containing sodium bicarbonate (18.5g). The mixture was stirred for 1.5h then concentrated to ca. 100ml and washed with ether. The aqueous portion was acidified with 2N-hydrochloric acid and extracted with ethyl acetate. The extracts were dried, concentrated to ca. 50ml and added dropwise to stirred cyclohexane (1.2l). The precipitated solid was collected by filtration, washed with cyclohexane and dried to give the title compound (40.7g), $[\alpha]_D$ +149° (c 0.76; Me_2SO).

Intermediate 40

[2S-[2α,5α,6β]]-N,N'-[1,2-Ethanediylbis[6[[[(1,1'-biphenyl)-2-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

1-Ethylpiperidine (1.96ml) then ethyl chloroformate (1.27ml) were added to a solution of Intermediate 39 (5.0g) in dichloromethane at -10°. The solution was

stirred for 30 min and ethylenediamine (1.26ml) was added dropwise. The mixture was allowed to warm to room temperature then stirred for 2h. The solution was successively washed with 2N-hydrochloric acid, brine solution, saturated aqueous sodium bicarbonate and brine solution then dried and evaporated to give a white foam. This was treated with ether to give the title compound as a white solid (3.98g), $[\alpha]_D$ +231° (c 0.43; Me_2SO).

Intermediate 41

[2R-[2α(R*),4β]]-4-[[(2-Aminoethyl)amino]carbonyl]-5,5-dimethyl-N-[[(4-dimethylamino)phenyl]methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

Ethyl chloroformate (6.41ml) was added to a stirred solution of benzylpenicillin N-ethylpiperidine salt (30g) in dichloromethane (500ml) at -10°. The reaction solution was stirred for 2h and was then washed with cold 0.2M phosphate buffer (pH7) and brine. A solution of 2-azidoethylamine (8.22g) in 4N-sodium hydroxide (16.8ml) containing cetyltrimethylammonium bromide (2.35g) was added. The mixture was stirred for 2h, then washed with water, saturated sodium bicarbonate solution, brine, 0.5N-hydrochloric acid, water and brine. The solution was dried and evaporated to afford an off-white foam. A portion of this material (15.4g) in dichloromethane (500ml) was treated with 4-(dimethylamino)benzylamine (10.7g) and triethylamine (14ml). The solution was stirred for 16h then washed sequentially with water and brine solution then dried and evaporated. The resulting solid was purified by chromatography on silica gel (Merck Art 9385, 500g). Appropriate fractions were combined to give a white foam. This was added to a stirred suspension of 10% palladium on charcoal (4.0g) in ethanol (800ml). The mixture was stirred under an atmosphere of hydrogen for 16h. The catalyst was then removed and the filtrate evaporated to afford the title compound (15.0g) as a white foam, $[\alpha]_D$ +53° (c 0.8; Me_2SO).

Intermediate 42

[2S-[2α,5α,6β]2'R-[2'α(R*)4β]]-3,3-Dimethyl-2-[[[[5,5-dimethyl-2-[2-[[[(4-dimethylamino)phenyl]methyl]amino]-2-oxo-1-[(phenylacetyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide

Pencillin G (3.76g), 1-hydroxybenzotriazole (1.93g) and then dicyclohexylcarbodiimide (2.58g) were added to a stirred solution of Intermediate 41 (5.0g) in tetrahydrofuran (300ml). The reaction solution was stirred for 16h, then filtered and the filtrate evaporated. The residue was suspended in ethyl acetate, filtered and the filtrate evaporated. The resulting solid was chromatographed on silica gel (Merck Art 9385, 300g) eluting with ethyl acetate-acetone (3:1). The appropriate fractions were combined to afford the title compound as a white foam (1.30g), $[\alpha]_D$ +173° (c 0.7; Me_2SO).

Intermediate 43

[2S-[2α,5α,6β]]-3,3,-Dimethyl-6-[(3-methyl-1-oxobutyl)amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

A solution of isovaleryl chloride (10ml) in acetone (50ml) was added dropwise over 10 min. to a stirred solution of 6-aminopenicillanic acid (18g) in water (100ml) containing sodium bicarbonate (14g). The solution was stirred for 1.5h then concentrated to a ca. 100ml and washed with ethyl acetate. The aqueous portion was acidified and extracted with ethyl acetate. The combined extracts were dried and evaporated to give a white foam. This was dissolved in ethyl acetate (50ml) and the solution was added to cyclohexane (1.0l). The precipitated solid was collected, washed with cyclohexane and dried to give the title compound as a white solid (20.8g), $[\alpha]_D$ + 214° (c 0.99; Me_2SO).

Intermediate 44

[2S-[2α,5α,6β]]-N,N'-[(2-Hydroxy-1,3-propanediyl)bis[3,3-dimethyl-6-[(3-methyl-1-oxobutyl)amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide]]

A solution of Intermediate 43 (5g) in dichloromethane (150ml) was cooled to -10° and treated with 1-ethylpiperidine (2.29ml) followed by ethyl chloroformate (1.6ml). The solution was stirred for 30 min. then extracted with 0.5M-phosphate buffer (pH7) and saturated brine. The organic extract was dried and the solution was treated with a suspension of 1,3-diamino-2-hydroxypropane (0.75g) in dichloromethane (50ml). After 2h the solution was successively washed with 0.5N-hydrochloric acid, saturated brine solution, saturated aqueous sodium bicarbonate and brine. The organic portion was dried and evaporated to give a foam. This was chromatographed on silica gel (Merck Art 9385, 50g) using chloroform - methanol (19:1). Appropriate fractions were combined to give the title compound as a white solid (0.99g), IR ν_{max} ($CHBr_3$) 1789, 1672 and 1516cm^{-1}.

Intermediate 45

[2R-(2α(R*),4β]-5,5-Dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinecarboxylic acid

1. H. T. Clark et al., The Chemistry of Penicillin, Princeton University Press, Princeton, 1949, p634.

2. J. Erikson et al., Science, 1990, 249, p527.

Intermediates 46-48 were prepared using the methodology of D. E. Kiely et al., J. Carbohydrate Chemists, 1986, 5(2), p183-197.

Intermediate 46

(2S,3R)-1,4-Diaminobutane-2,3-diol

Intermediate 47

(R,R)-1,4-Diaminobutan-2,3-diol

Intermediate 48

(S,S)1,4-Diaminobutane-2,3-diol dihydrochloride

Example 1

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

A solution of ethylamine (0.4ml) in dichloromethane (3.6ml) was added to a stirred solution of Intermediate 1 (2.0g) in dichloromethane (100ml). The solution was stirred for 4.5h and further ethylamine (0.4ml) in dichloromethane was added. The solution was stored at 0-5^0 for 2.5 days during which time a solid was deposited. The solid was collected by filtration, washed with cold dichloromethane and dried to give a white solid (2.1g) which crystallised from acetonitrile to give the title compound in 3 crops (total 1.57g), mp 186.5-187.5^0, $[\alpha]_D$ +45.5^0 (c 1.0, MeOH), ^{1}H nmr (DMSO-d_6) δ 0.99 (4H), 1.13 (6H), 1.46 (6H), 3.0-3.25 (8H), 3.40 (2H), 3.50 (4H), 3.78 (2H), 4.30 (2H), 4.82 (2H), 7.22 (10H), 7.95 (4H) and 8.28 (2H).

Example 2

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]]

Benzylamine (4ml) was added to a stirred solution of Intermediate 1 (4.16g) in dichloromethane (150ml). The solution was stirred for 4 days then successively washed with 0.5N-hydrochloric acid, water, saturated sodium bicarbonate, water and saturated brine. The dried solution was evaporated to give a white foam (6.77g) which crystallised from hot acetonitrile (450ml) to afford the title compound as white prisms, mp 198^0, $[\alpha]_D$ + 39^0 (c 1.0, MeOH), ^{1}H nmr (DMSO-d_6) δ 1.15 (6H), 1.50 (6H), 3.17 (4H), 3.43 (2H), 3.52 (4H), 3.83 (2H), 4.27 (4H), 4.44 (2H), 4.89 (2H), 7.13-7.33 (20H), 7.97 (2H), 8.37 (2H) and 8.53 (2H).

Example 3

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N,N-dimethyl-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

A solution of Intermediate 1 (504mg) and dimethylamine (220mg) in dichloromethane (25ml) was stirred for 6h during which time a white solid was deposited. The mixture was evaporated to dryness and the residue (675mg) crystallised from dichloromethane to give the title compound as white prisms (323mg), mp 124.5-128^0, $[\alpha]_D$ + 61^0 (c 1.0, MeOH), ^{1}H nmr (DMSO-d_6) δ 1.10 (6H), 1.47 (6H), 2.78 (6H), 2.96 (6H), 3.0-3.3 (4H), 3.42 (2H), 3.45 (4H), 3.8-3.9 (2H), 4.80 (4H), 7.1-7.3 (10H), 8.01 (2H) and 8.58 (2H).

Example 4

[2R-[2α(R*),4β]]-4,4'-1,2-[Ethanediylbis[aminocarbonyl]bis[N-(cyclohexylmethyl)-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazoleacetamide]]

Cyclohexanemethylamine (0.38ml) was added to a solution of Intermediate 1 (502mg) in dichloromethane (25ml). The solution was stirred for 21h during which time a solid was precipitated. This was collected by filtration, washed with cold dichloromethane and ether and dried (416mg). This material was crystallised from acetonitrile to provide the title compound as white prisms (303mg), mp 185-186^0, $[\alpha]_D$ + 29^0 (c 1.0, MeOH), ^{1}H nmr (DMSO-d_6) δ 0.7-1.7 (22H), 1.13 (6H), 1.50 (6H), 2.86 (4H), 3.15 (4H), 3.41 (2H), 3.49 (4H), 3.78 (2H), 4.35 (2H), 4.81 (2H), 7.1-7.3 (10H), 7.94 (4H) and 8.30 (2H).

Example 5

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-[(4-(trifluoromethyl) phenyl)methyl]-2-thiazolidineacetamide]]

4-(Trifluoromethyl)benzylamine (0.42ml) was added to a stirred solution of Intermediate 1 (502mg) in dichloromethane (25ml). The solution was stirred for 8 days during which time a solid was deposited. This was collected by filtration, washed with dichloromethane and ether and dried (238mg). Crystallisation from acetonitrile afforded the title compound as white prisms (180mg), mp 186, $[\alpha]_D$ +4^0 (c 1.07, MeOH), ^{1}H nmr (DMSO-d_6) δ 1.15 (6H), 1.50 (6H), 3.18 (4H), 3.45 (2H),

3.52 (4H), 3.88 (2H), 4.34 (4H), 4.43 (2H), 4.88 (2H), 7.25 (10H), 7.4-7.65 (8H), 8.02 (2H), 8.44 (2H) and 8.68 (2H).

Example 6

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(2-pyridinylmethyl)-2-thiazolidineacetamide]]

2-(Aminomethyl)pyridine (0.3ml) was added to a solution of Intermediate 1 (503mg) in dichloromethane (25ml). The solution was stirred for 18h during which time a solid precipitated. The solid was washed with dichloromethane and ether and dried (552mg). Crystallisation from acetonitrile afford the title compound as white prisms (446mg), mp 139^0, $[\alpha]_D$ +15.4^0 (c 1.08, MeOH), ^{1}H nmr (DMSO-d_6) δ 1.14 (6H), 1.50 (6H), 3.16 (4H), 3.45 (2H), 3.54 (4H), 3.87 (2H), 4.35 (4H), 4.47 (2H), 4.92 (2H), 7.1-7.35 (14H), 7.67 (2H), 8.01 (2H), 8.35-8.5 (4H) and 8.65 (2H).

Example 7

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(2,2,2-trifluoroethyl)-2-thiazolidineacetamide]]

2,2,2-Trifluoroethylamine (0.23ml) was added to a stirred solution of Intermediate 1 (503mg) in dichloromethane (25ml). The solution was stirred for a total of 24 days during the course of which additional aliquots of 2,2,2-trifluoroethylamine (total 1.33ml) were added at intervals. The solid which had precipitated was collected by filtration, washed with dichloromethane and ether and dried (123mg). This was treated with dichloromethane to give a white solid (73mg). The original reaction liquors also deposited further solid upon standing (84mg). The major portions of the two solids were combined (123mg) and subjected to preparative HPLC purification on an S5-ODS-2 column using aqueous acetonitrile as eluant. The major component was evaporated to give a white solid which crystallised from dichloromethane to provide the title compound as white prisms (52mg), mp 177.5-179^0, ^{1}H nmr (DMSO-d_6) δ 1.12 (6H), 1.48 (6H), 3.16 (4H),

3.42 (2H), 3.52 (4H), 3.75-4.0 (6H), 4.44 (2H), 4.84 (2H), 7.15-7.3 (10H), 8.00 (2H), 8.42 (2H) and 8.72 (2H).

Example 8

[2R-[2α(R*),4β]]-N,N'-[1,2-Ethanediylbis[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-(1-piperidinyl)ethyl]-4-thiazolidinecarboxamide]]

Piperidine (0.3ml) was added to a stirred solution of Intermediate 1 (503mg) in dichloromethane (25ml). The solution was stirred for 5 days during which time a solid was deposited. This was collected, washed with dichloromethane and ether and dried (271mg). Crystallisation from acetonitrile afforded the title compound as white prisms (208mg), mp 146^0, ^{1}H nmr (DMSO-d_6) δ 1.05-1.6 (12H), 1.10 (6H), 1.46 (6H), 2.95-3.6 (14H), 3.45 (4H), 3.82 (2H), 4.81 (4H), 7.1-7.3 (10H), 7.99 (2H) and 8.64 (2H).

Example 9

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(2-phenylethyl)-2-thiazolidineacetamide]]

2-Phenylethylamine (0.54ml) was added to a solution of Intermediate 1 (500mg) in dry dichloromethane (25ml). The reaction mixture was stirred for 2.5 days then evaporated to dryness. The residue was stirred with ether to give a white solid which was collected and dried (549mg). Crystallisation from acetonitrile afforded the title compound as white prisms (393mg), m.p. 167-168^0, $[\alpha]_D$ +31^0 (c 1.13; MeOH), ^{1}H nmr (DMSO-d_6) δ 1.13 (6H), 1.45 (6H), 2.28 (4H), 3.0-3.3 (8H), 3.41 (2H), 3.50 (4H), 3.77 (2H), 4.34 (2H), 4.83 (2H), 7.1-7.35 (20H), 7.97 (2H), 8.10 (2H) and 8.32 (2H).

Example 10

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(3-methyl-1-oxobutyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]]

Benzylamine (0.17ml) was added to a stirred solution of Intermediate 2 (200mg) in dry chloromethane (15ml). The solution was set aside at $+21^0$ for 3 days then additional benzylamine (0.07ml) was added. The mixture was left for a further 4 days then evaporated to dryness. The residue was washed with ether by decantation and then crystallised from acetonitrile to give the title compound as white prisms (126mg), $[\alpha]_D$ $+59^0$ (c 1.0; MeOH), ^{1}H nmr (DMSO-d_6) δ 0.82 (12H), 1.10 (6H), 1.47 (6H), 1.85-2.10 (6H), 2.9-3.4 (4H), 3.40 (2H), 3.75 (2H), 4.26 (4H), 4.42 (2H), 4.86 (2H), 7.20 (10H), 8.01 (4H) and 8.48 (2H).

Example 11

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(3-phenyl-1-oxopropyl)amino]-2-thiazolidineacetamide]]

3-Phenylpropionic acid (210mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (300mg) were added to a stirred solution of Intermediate 5 (380mg) in dichloromethane (60ml). The mixture was stirred for 2h during which a solid was precipitated. This was collected, washed with ether and dried to give the title compound as white crystalline solid (250mg), m.p. 158-159^0, $[\alpha]_D$ $+59^0$ (c 1.0; MeOH), ^{1}H nmr (DMSO-d_6) δ 0.98 (6H), 1.12 (6H), 1.48 (6H), 2.43 (4H), 2.80 (4H), 3.03 (4H), 3.17 (4H), 3.40 (2H), 3.72 (2H), 4.31 (2H), 4.80 (2H), 7.18 (10H), 7.94 (2H), 8.12 (2H) and 8.16 (2H).

Example 12

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[(4-methoxyphenyl)methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

4-Methoxybenzylamine (0.39g) was added to a stirred solution of Intermediate 1 (505mg) in dichloromethane (25ml) under an atmosphere of nitrogen. The solution was stirred for 5 days then evaporated to give an off-white foam which was treated with ether to give a white solid which was collected and dried (654mg). This material was crystallised from acetonitrile to give the title compound as white prisms (391mg), m.p. 158-159°, $[\alpha]_D$ +43° (c 1.14; MeOH), ^{1}H nmr (DMSO-d_6)

1.13 (6H), 1.50 (6H), 3.16 (4H), 3.42 (2H0, 3.52 (4H), 3.72 (6H), 3.88 (2H), 4.05-4.30 (4H), 4.41 (2H), 4.88 (2H), 6.82 (4H), 7.15 (4H), 7.18-7.20 (10H), 7.98 (2H), 8.36 (2H) and 8.45 (2H).

Example 13

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

A solution of glycine t-butyl ester hydrochloride (490mg) and triethylamine (0.41ml) in dichloromethane (10ml) was added to a stirred solution of Intermediate 1 (506mg) in dry dichloromethane (506mg). The solution was stirred for 7 days then evaporated to give a white foam. This was stirred with ether to give a white solid which was collected and dried (1.05g). This material was purified by column chromatography on silica gel (Merck Art 9385, 40g) using chloroform-methanol (19:1) as eluant to give an off white foam (523mg) which crystallised from acetonitrile to afford the title compound as white prisms (356mg), m.p. 133^0, $[\alpha]_D$ $+35^0$ (c 1.16; MeOH), ^{1}H nmr (DMSO-d_6) 1.12 (6H), 1.40 (18H), 1.47 (6H), 3.15 (4H), 3.42 (2H), 3.52 (4H), 3.64-3.85 (6H), 4.45 (2H), 4.87 (2H), 7.10-7.35 (10H), 7.98 (2H) and 8.32 (4H).

Example 14

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[[(5-methyl-3-phenyl-4-isoxazolyl)carbonyl]amino]-2-thiazolidineacetamide]]

Ethylamine (0.13ml) was added to a solution of Intermediate 6 (200mg) in dichloromethane (10ml). The solution was stored at $+21^0$ for 16h then evaporated to dryness. The residue was crystallised from acetonitrile to furnish the title compound as white prisms (148mg), m.p. 173-173.5°, $[\alpha]_D$ +32° (c 0.73; Me_2SO), ^{1}H nmr (DMSO-d_6) 1.02 (6H), 1.14 (6H), 1.52 (6H), 2.5 (DMSO + 6H), 2.94-3.23 (8H), 3.25 (2H), 3.97 (2H), 4.54 (2H), 4.88 (2H), 7.32-7.5 (6H), 7.69-7.83 (4H), 8.04-8.26 (4H) and 8.82 (2H).

Example 15

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(phenoxyacetyl)amino]-2-thiazolidineacetamide]]

Ethylenediamine (0.03ml), 1 - hydroxybenzotriazole hydrate (149mg) and N, N' - dicyclohexylcarbodiimide (227mg) were successively added to a stirred solution of Intermediate 7 (400mg) in dry tetrahydrofuran (5ml). The mixture was stirred for 3h during which time a solid was deposited. Ethyl acetate (10ml) was added and the mixture filtered. The filtrate was washed with water, saturated sodium bicarbonate solution and brine solution, then dried and evaporated to give a white solid (320mg). This was purified by chromatography on silica gel using ethyl acetate - acetone - dichloromethane (5:3:2) to give the title compound as a white solid (75mg), mp. 127-128°, ^{1}Hnmr ($CDCl_3$) 1.15 (6H), 1.30 (6H), 1.58 (6H), 3.15 - 3.65 (12H), 4.50 (4H), 4.60 (2H), 4.88 (2H), 6.58 (2H), 6.92 (6H), 7.01 (2H), 7.38 (4H) and 7.58 (2H).

Example 16

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5- dimethyl-α-[(((phenyl)methyl)sulphonyl)amino]-2-thiazolidineacetamide]]

Triethylamine (0.2ml) then α-toluenesulphonyl chloride (260mg) were added to a stirred solution of Intermediate 5 (354mg) in dichloromethane (25ml) at 0-5°. The mixture was allowed to warm to room temperature over 4½h then successively washed with water, saturated sodium bicarbonate solution and brine solution. The solution was dried and evaporated and the residue purified by chromatography on a column of silica gel (Merck Art 9385, 10g) using 5% ethanol in ethyl acetate. Appropriate fractions were combined to give the title compound as a white solid (60mg). Crystallisation from ethyl acetate provided an analytical sample, mp. 147-148°, $[\alpha]_D$ + 100° (c 0.56, Me_2SO), ^{1}H nmr (DMSO-d_6) 0.90-1.15 (12H), 1.52 (6H), 3.0-3.3 (8H), 3.45 (2H), 4.02 (2H), 4.31 (2H), 4.60 (2H), 4.76 (2H), 7.32 (10H), 7.45 (2H) and 8.16 (4H).

Example 17

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2- oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-α-[(2-phenyl-1-oxoethyl)amino]-N-[(2-pyridinyl)methyl]-2-thiazolidineacetamide

Benzylamine (1.1ml) and 2 - aminomethylpyridine (1.05ml) were added to a stirred solution of Intermediate 1 (1.73g) in dry dichlorometha· '50ml). The solution was set aside for 3 days during which time a solid precipi..ed. The solid was collected, washed with dichloromethane and ether and dried (1.80g), then purified by column chromatography on silica gel (Merck Art 9385) eluting with 5-10% ethanol in chloroform. Appropriate fractions were combined to give the title compound (404mg) which crystallised from acetonitrile as white prisms (312mg), m.p. 186-187°, $[\alpha]_D$ + 22° (c 0.99; MeOH), ^{1}Hnmr (DMSO-d_6) 1.13 (6H), 1.49 (6H), 3.18 (4H), 3.46 (2H), 3.50 (4H), 3.81 (2H), 4.16 - 4.40 (4H), 4.47 (2H), 4.90 (2H), 7.15 - 7.40 (17H), 7.65 (1H), 7.98 (2H), 8.35 (2H), 8.49 (2H) and 8.61 (1H).

Example 18

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2- oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-(phenylmethyl)-α-[[1-oxo-2-(2-pyridinyl)ethyl]amino]-2-thiazolidineacetamide

Phenylacetic acid (320mg), 2 - pyridylacetic acid hydrochloride (406mg), triethylamine (0.33ml) and 1 - (3 - dimethylaminopropyl) - 3 - ethylcarbodiimide hydrochloride (1.92g) were successively added to a solution of Intermediate 9 (1.57g) in dioxan (35ml) - water (5ml). The solution was stirred for 4.5h, then partitioned between saturated sodium bicarbonate (70ml) and ethyl acetate (100ml). The aqueous layer was separated and re-extracted with ethyl acetate (100ml). The combined organic extracts were washed with water and brine solution then dried and evaporated to give a yellow foam (2.28g). This was purified by chromatography on

silica gel (Merck Art 9385) eluting with 3 - 15% - ethanol in chloroform. Appropriate fractions were combined to give the title compound as a pale yellow solid (547mg) which crystallised from acetonitrile to give white prisms (168mg), m.p. 169 - 170°, $[\alpha]_D$ + 49° (c 1.095; MeOH), ^{1}Hnmr (DMSO-d_6) 1.16 (6H), 1.52 (6H), 3.18 (4H), 3.40 - 3.58 (4H), 3.74 (2H), 4.90 (2H), 7.1 - 7.34 (17H), 7.38 (1H), 7.68 (1H), 8.0 (2H), 8.41 (2H), 8.54 (2H) and 8.65 (1H).

Example 19

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbon . ı]bis[α-[[(4-chlorophenyl)acetyl]amino]-5,5-dimethyl-N-(2-pyridinylmethyl)-2-thiazolidineacetamide]]

4-Chlorophenylacetic acid (266mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (313mg) were added to a stirred solution of Intermediate 11 (500mg) in dichloromethane (40ml). The solution was stirred at +21° for 3.5h, then washed with water and sodium bicarbonate. The combined aqueous washings were back-extracted with dichloromethane and the combined organic portions were dried and evaporated. The residue was chromatographed on a column of silica gel (Fluka 60; 50g) using ethyl acetate-ethanol (9:1 then 5:1). Appropriate fractions were combined to give the title compound as a white solid (170mg). Crystallisation from acetonitrile afforded white prisms, m.p. 132-133°, $[\alpha]_D$ +22° (c 0.5; MeOH), ^{1}Hnmr (DMSO - d_6) δ 1.15 (6H), 1.49 (6H), 3.0 - 3.3 (4H), 3.44 (2H), 3.53 (4H), 3.87 (2H), 4.35 (4H), 4.46 (2H), 4.91 (2H), 7.15 - 7.4 (12H), 7.68 (2H), 8.03 (2H), 8.4 - 8.5 (4H) and 8.65 (2H).

Example 20

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5- dimethyl-α-[[[(1,1'-biphenyl)-2-yl]carbonyl]amino]-N-phenylmethyl-2-thiazolidineacetamide]]

2-Phenylbenzoic acid (233mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (257mg) were added to a stirred solution of Intermediate 9 (360mg) in dichloromethane (30ml). The mixture was stirred for 19h

when additional 2-phenylbenzoic acid (105mg) and 1-(3-dimethlyaminopropyl)-3-ethylcarbodiimide hydrochloride (205mg) were added. The mixture was stirred for a further 7h, then diluted with dichloromethane and washed with water and sodium bicarbonate. The aqueous washings were back-extracted with dichloromethane and the combined organic extracts then dried and evaporated. The residue was chromatographed on silica gel (Fluka 60, 50g) using ethyl acetate followed by ethyl acetate - acetone (4:1) to give the title compound as a white solid (116mg). A portion of this material was crystallised from acetonitrile to afford white prisms, m.p. 180-181°, $[\alpha]_D$ + 75° (c 1.0; MeOH), ^{1}H nmr (DMSO-d_6) 1.17 (6H), 1.53 (6H), 3.1-3.4 (4H), 3.45 (2H), 3.87 (2H), 4.29 (4H), 4.48 (2H), 4.97 (2H), 7.15-7.6 (28H), 8.18 (2H), 8.41 (2H) and 8.70 (2H).

Example 21

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[(4-chlorophenyl)methyl]-5,5-dimethyl-α-[(2-pyridinylacetyl)amino]-2-thiazolidineacetamide]]

2-Pyridylacetic acid hydrochloride (127 mg), a solution of triethylamine (0.1ml) in dichloromethane (10ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (191mg) were added in turn to a stirred solution of Intermediate 13 (240mg) in dichloromethane (30ml) under an atmosphere of nitrogen. The solution was stirred for 23h and additional 2-pyridylacetic acid hydrochloride (62mg), triethylamine (0.05ml) in dichloromethane (5ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (108mg) were added. The solution was stirred for a further 3.5h, then washed with saturated sodium bicarbonate solution and brine, dried and evaporated to give a yellow solid (339mg). This was purified by chromatography on silica (Merck Art 9385, 35g) using chloroform-methanol (9:1) to afford the title compound (180mg) which crystallised from acetonitrile as white prisms (86mg), m.p. 156-159°, $[\alpha]_D$ + 52.5° (c 0.99; MeOH), ^{1}H nmr (DMSO-d_6) 1.15 (6H), 1.48 (6H), 3.17 (4H), 3.44 (2H), 3.71 (4H),

3.89 (2H), 4.26 (4H), 4.42 (2H), 4.89 (2H), 7.15-7.4 (12H), 7.68 (2H), 8.03 (2H), 8.43 (2H), 8.51 (2H) and 8.67 (2H).

Example 22

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[(2,4-dichlorophenyl)methyl]-5,5-dimethyl-α-[(2-pyridinylacetyl)amino]-2-thiazolidineacetamide]]

2-Pyridylacetic acid hydrochloride (349mg), a solution of triethylamine (0.28ml) in dichloromethane (20ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (520mg) were added to a solution of Intermediate 15 (729mg) in dichloromethane (80ml). The solution was stirred under an atmosphere of nitrogen for 22h when further 2-pyridylacetic acid hydrochloride (174mg), triethylamine (0.14ml) in dichloromethane (5ml) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (280mg) were added. Stirring was continued for a futher 3h and the solution washed with saturated sodium bicarbonate and brine. The dried solution was evaporated to give a yellow solid (1.07g) which was subjected to chromatography on silica gel (Merck Art 9385, 100g). Elution with chloroform-methanol (9:1) gave the title compound as a pale yellow solid (577mg). Crystallisation from acetonitrile afforded white prisms (302mg), m.p. 139.5-142°, $[\alpha]_D$ + 15° (c 0.92; MeOH), ^{1}H nmr (DMSO-d_6) 1.15 (6H), 1.50 (6H), 3.18 (4H), 3.45 (2H), 3.72 (4H), 3.92 (2H), 4.30 (4H), 4.46 (2H), 4.90 (2H), 7.2-7.45 (8H), 7.60 (2H), 7.69 (2H), 8.05 (2H), 8.44 (2H), 8.55 (2H) and 8.73 (2H).

Example 23

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[[(4-dimethylamino)phenyl]methyl]-α[(phenylacetyl)amino]-2-thiazolidineacetamide]]

4-(Dimethylamino) benzylamine dihydrochloride (644mg) and triethylamine (0.41ml) were added to a stirred solution of Intermediate 1 (503mg) in dichloromethane (50ml). The solution was stirred under an atmosphere of nitrogen

for 8 days with further portions of 4 - (dimethylamino)benzylamine dihydrochloride (644mg) and triethlyamine (1.0ml) in dichloromethane (20ml) being added after 5 and 7 days. The reaction mixture was filtered and evaporated to an off-white solid (2.49g). This was dissolved in ethyl acetate and the solution washed with water, saturated sodium bicarbonate solution and brine, then dried and evaporated to a pale brown solid (595mg). Crystallisation twice from acetonitrile afforded the title compound as white prisms (329mg), m.p. 172-174°, $[\alpha]_D$ + 49° (c 1.14; $CHCl_3$), ^1H nmr (DMSO-d_6) 1.13 (6H), 1.47 (6H), 2.85 (12H), 3.16 (4H), 3.42 (2H), 3.50 (4H), 3.82 (2H), 4.0-4.25 (4H), 4.40 (2H), 4.87 (2H), 6.62 (4H), 7.03 (4H), 7.1-7.3 (10H), 7.97 (2H) and 8.3-8.4 (4H).

Example 24

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[(N-methylamino) carbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]]

Benzylamine (0.3ml) was added to a stirred solution of Intermediate 16 in dry dichloromethane (25ml). The solution was stirred under an atmosphere of nitrogen for 5 days, then evaporated to dryness (759mg). The residue was purified by column chromatography on silica gel (Merck Art 9385, 75g) using ethyl acetate-acetone (2:1) to give the title compound as a cream solid (252mg). An analytical sample was obtained by preparative HPLC (S5 - ODS.2 column using 55% acetonitrile in water), m.p. ca 129°, $[\alpha]_D$ + 45° (c 0.87; MeOH).

Example 25

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-N-(phenylmethyl)-α-[[[(1,1'-biphenyl)-2-yl]carbonyl] amino]-2-thiazolidine acetamide]]

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (320mg) and 2-phenylbenzoic acid (330mg) were added to a stirred solution of Intermediate 5 (450mg) in dichloromethane (25ml). The mixture was stirred for 19h then washed with water and saturated sodium bicarbonate. The dried solution was evaporated

and the residue (635mg) was chromatographed on a column of silica gel (Merck Art 9385, 50g) using ethyl acetate followed by ethyl acetate-acetone (4:1) to give the title compound as an amorphous white solid (155mg), $[\alpha]_D$ +48° (c 0.56; Me_2SO), ^1H nmr (DMSO-d_6) δ 1.00 (6H), 1.14 (6H), 2.94-3.14 (4H), 3.14-3.30 (4H), 3.43 (2H), 3.70-3.88 (2H), 4.35 (2H), 4.90 (2H), 7.2-7.6 (18H), 7.84 (2H), 8.15 (2H) and 8.55 (2H).

Example 26

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-N-[(2,4-Dichlorophenyl)methyl]-5,5-dimethyl-4-[[[[[[5,5,-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-α-[[1-oxo-2-(2-pyridinyl)ethyl]amino-2-thiazolidineacetamide

A solution of 45% hydrogen bromide in acetic acid (4.1ml) in dichloromethane (25ml) was added to a stirred solution of Intermediate 20 (0.80g) in dichloromethane (25ml). The solution was stirred for 40 min then poured with stirring into light petroleum (bp. 40-60°) (500ml). The precipitated solid was collected by filtration, washed with ether and dried. The resulting pink solid was partitioned between ethyl acetate and sodium bicarbonate solution and the organic portion dried and evaporated to give an off-white solid (0.67g). This material was further purified by flash chromatography on silica gel using dichloromethane (15:1) to give a white foam (0.38g). The bulk of this (368mg) was dissolved in anhydrous dichloromethane (45ml) and the solution treated with 2-pyridylacetic acid (81mg), triethylamine (65μl) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (122mg). The mixture was stirred for 6h then diluted with dichloromethane and washed with water, sodium bicarbonate solution and brine. The dried solution was evaporated to a yellow foam which was chromatographed on silica gel using dichloromethane-methanol (15:1) to furnish a white solid (280mg). A portion of this material (140mg) was further purified by preparative HPLC (S5-ODS2 column eluting with 50%-acetonitrile in water) to give the title compound as a freeze-dried white solid (90mg), $[\alpha]_D$ +53° (c 0.61; Me_2SO), ^1H nmr (DMSO-d_6)

δ 1.15 (6H), 1.50 (6H), 3.20 (4H), 3.4-3.55 (2H), 3.50 (2H), 3.75 (2H), 3.8-4.0 (2H), 4.15-4.4 (4H), 4.4-4.5 (2H), 4.90 (2H), 7.15-7.4 (14H), 7.60 (1H), 7.70 (1H), 8.00 (2H), 8.35-8.50 (2H), 8.50-8.60 (2H) and 8.75 (1H).

Example 27

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5,-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-α-[[(phenylmethoxy)carbonyl]amino]-N-[(2-pyridinyl)methyl]-2-thiazolidineacetamide

2-Aminomethylpyridine (0.49ml) was added to a stirred solution of Intermediate 19 (1.58g) in dichloromethane (40ml) under an atmosphere of nitrogen. The solution was stirred for 72h then evaporated to an orange foam. This was purified by chromatography on a column of silica gel (Merck Art 9385) using dichloromethane-methanol (19:1) to give the title compound as an off-white foam (1.50g). A portion (290mg) of this material was crystallised from acetonitrile to give white prisms (200mg), mp 119-124°, $[\alpha]_D$ +65° (c 1.10, Me_2SO), ^1H nmr (DMSO-d_6) δ 1.13 (6H), 1.48 (3H), 1.50 (3H), 3.03-3.18 (4H), 3.40-3.48 (2H), 3.51 (2H), 3.78-3.93 (2H), 4.18 (1H), 4.26 (2H), 4.35 (2H), 4.44 (1H), 4.81-4.93 (2H), 5.06 (2H), 7.15-7.40 (17H), 7.51 (1H), 7.71 (1H), 7.98 (1H), 8.07 (1H), 8.39 (1H), 8.48 (1H), 8.55 (1H) and 8.69 (1H).

Example 28

[2R-[2α(R*),4β]-4,4'-Bis[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-((2-N,N-dipropylamino)ethyl)]-2-thiazolidineacetamide]]

2-N,N-Dipropylaminoethylamine (415mg) was added to a stirred solution of Intermediate 1 (500mg) in dichloromethane (20ml) under an atmosphere of nitrogen. The mixture was stirred for 20h then evaporated to a brown gum. This was purified by chromatography on silica gel (Merck Art 9385) using chloroform-methanol-concentrated ammonia solution (110:10:1) to give a gum which crystallised from

acetonitrile to afford the title compound as white prisms (402mg), mp 192-198°, $[\alpha]_D$ +88° (c 0.74; Me_2SO), ^1H nmr (DMSO-d_6) δ 0.81 (12H), 1.12 (6H), 1.26-1.45 (8H), 1.46 (6H), 2.22-2.44 (12H), 3.00-3.29 (8H), 3.40 (2H), 3.49 (4H), 3.79 (2H), 4.30 (2H), 4.81 (2H), 7.22 (10H), 7.76 (2H), 7.98 (2H) and 8.32 (2H).

Example 29

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-α-[[2-(4-Chlorophenyl)-1-oxoethyl]amino]-5,5-dimethyl-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[(2-pyridinyl)methyl]-2-thiazolidineacetamide

The product of Example 27 (1.16g) was treated with 45%-hydrogen bromide in acetic acid (25ml). The mixture was stirred for 10 min and the solution added to ether (100ml). The precipiated solid was collected then redissolved in methanol and solid sodium bicarbonate added. The mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in ethyl acetate and the solution washed several times with saturated aqueous sodium bicarbonate, then dried and evaporated to give a pale yellow solid (0.90g). This was purified by column chromatography on silica gel (Merck Art 9385, 100g) using dichloromethane-methanol (19:1) to give an off-white solid (360mg). The bulk of this (300mg) was dissolved in dry dichloromethane (24ml) and the solution treated with 4-chlorophenylacetic acid (72mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (81mg). The mixture was stirred for 3h under an atmosphere of nitrogen then diluted with dichloromethane (150ml) and the solution washed sequentially with water, bicarbonate and brine. The dried solution was evaporated to a gum (360mg) which crystallised from acetonitrile to afford the title compound as white prisms, (140mg), mp 146-149.5°, $[\alpha]_D$ +65° (c 1.03, Me_2SO), ^1H nmr (DMSO-d_6) 1.15 (6H), 1.50 (6H), 3.02-3.19 (4H), 3.43 (2H), 3.52 (4H), 3.78-3.96 (2H), 4.26 (2H), 4.34 (2H), 4.38-4.52 (2H), 4.83-4.96 (2H), 7.14-7.36 (16H), 7.68 (1H), 8.01 (2H), 8.40 (1H), 8.43-8.51 (2H), 8.56 (1H) and 8.67 (1H).

Example 30

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[[(2-phenylcyclopropyl)carbonyl]amino]-N-(phenylmethyl)-2-thiazolidineacetamide]]

Benzylamine (1.5ml) was added to a solution of Intermediate 23 (1.05g) in dichloromethane (20ml). The solution was stored at room temperature for 12h then evaporated to dryness. The residue was triturated with ether to give an off-white solid (1.14g) which showed 3 major components by TLC. This material was purified by chromatography on a column of silica gel (Merck Art 9385, 100g) using chloroform-methanol-concentrated ammonia solution (90:4.5:0.5). The least polar fraction was evaporated to give a white solid (143mg) which crystallised from 2-propanol to give the title compound isomer A as white prisms (99mg), mp 164-166°, $[\alpha]_D$ +100° (c 0.83, MeOH). The fraction with intermediate polarity was evaporated to give a white solid (319mg) which crystallised from 2-propanol to give the title compound isomer B as white prisms (142mg), mp 155-158°, $[\alpha]_D$ +95° (c 0.82, MeOH). The most polar fraction was evaporated to give a white solid (211mg) which crystallised from 2-propanol to give the title compound isomer C as white prisms (147mg), mp 145-148°, $[\alpha]_D$ +61° (c 0.86, MeOH).

Example 31

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[[(3-dimethylamino)phenyl]methyl]-α-[(phenylacetyl) amino]-2-thiazolidineacetamide]]

3-N,N-Dimethylaminobenzylamine dihydrochloride (0.98g) and triethylamine (1.22ml) were added to a stirred solution of Intermediate 1 (0.51g) in dichloromethane (25ml). The solution was stirred for 48h, then washed with water and brine, dried and evaporated (0.92g). This was purified by column chromatography on silica gel (Merck Art 9385, 92g), eluting with ethyl acetate containing 20% acetone followed by 20-33% methanol in ethyl acetate. Appropriate fractions were combined to give a pale yellow solid (550mg) which crystallised from acetontrile to give the title compound as white prisms (250mg), mp 159-162°, $[\alpha]_D$

+40° (c 1.03, MeOH), ^{1}H nmr (DMSO-d_6) 1.13 (6H), 1.49 (6H), 2.86 (12H), 3.16 (4H), 3.43 (2H), 3.52 (4H), 3.83 (2H), 4.21 (4H), 4.44 (2H), 4.89 (2H), 6.48-6.65 (6H), 7.02-7.30 (12H), 7.99 (2H), 8.37 (2H) and 8.49 (2H).

Example 32

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α[[(3-methyl)phenylacetyl]amino]-2-thiazolidineacetamide]]

A 10% solution of ethylamine in dichloromethane (0.75ml) was added to a stirred solution of Intermediate 32 (150mg) in dichloromethane (8ml). The mixture was stirred for 16h, then evaporated to give the title compound as a solid, which crystallised from acetonitrile as white prisms (95mg), mp 170-172°, $[\alpha]_D$ +88° (c 0.5, Me_2SO), ^{1}H nmr (DMSO-d_6) 0.95 (6H), 1.10 (6H), 1.50 (6H), 2.25 (6H), 3.05 (4H), 3.15 (4H), 3.45 (4H), 3.75 (2H), 4.30 (2H), 4.85 (2H), 6.95-7.20 (8H), 7.95 (4H) and 8.25 (2H).

Example 33

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(2-thienylacetyl)amino]-2-thiazolidineacetamide]]

A 10% solution of ethylamine in dichloromethane (0.75ml) was added to a stirred solution of Intermediate 33 (150mg) in dichloromethane (8ml). The mixture was stirred for 8h, then evaporated to a solid, which crystallised from acetonitrile-petroleum ether (40-60°) to giuve the title compound as white prisms (87mg), mp 159-161°, $[\alpha]_D$ +82° (c 0.6; Me_2SO), ^{1}H nmr (DMSO-d_6) 1.00 (6H), 1.10 (6H), 1.50 (6H), 3.05 (4H), 3.15 (4H), 3.30 (2H), 3.80 (6H), 4.30 (2H), 4.80 (2H), 6.90 (4H), 7.30 (2H), 7.95 (4H) and 8.25 (2H).

Example 34

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[α-[[(3-chloro)phenylacetyl]amino]-N-ethyl-5,5-dimethyl-2-thiazolidineacetamide]]

A 10% solution of ethylamine in dichloromethane (0.75ml) was added to a stirred solution of Intermediate 34 (150mg) in dichloromethane (5ml). The mixture was stirred for 20h, then evaporated to a solid, which crystallised from acetonitrile to afford the title compound as a white solid (101mg), mp 173-175° $[\alpha]_D$ +85° (c 0.6, Me_2SO), ^1H nmr 1.00 (6H), 1.15 (6H), 1.50 (6H), 3.05 (4H), 3.20 (4H), 3.45 (2H), 3.50 (4H), 3.80 (2H), 4.35 (2H), 4.80 (2H), 7.00 (2H) and 7.25 (1H).

Example 35

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[2-(N,N-dimethylamino)ethyl]-α-[(2-phenyl-1-oxoethyl)amino]-2-thiazolidineacetamide

2-(Dimethylamino)-ethylamine (0.2ml) was added to a stirred suspension of Intermediate 24 (500mg) in dichloromethane (20ml). The mixture was stirred for 24h then evaporated to a solid. The solid was triturated with ether (30ml) then filtered. The collected solid was crystallised from ethylacetate-acetonitrile to afford the title compound as a white solid (328mg), mp 189-191°, $[\alpha]_D$ +83° (c 0.5, Me_2SO), ^1H nmr (DMSO-d_6) 1.15 (6H), 1.47 (3H), 1.50 (3H), 2.07 (3H), 2.10 (3H), 2.24 (2H), 3.20 (6H), 3.42 (1H), 3.45 (1H), 3.80 (2H), 4.27 (2H), 4.33 (1H), 4.43 (1H), 4.84 (1H), 4.88 (1H), 7.25 (15H), 7.82 (1H), 7.94 (2H), 8.27 (1H), 8.35 (1H) and 8.51 (1H).

Example 36

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[2-(1-piperidinyl)ethyl]-α-[(2-phenyl-1-oxoethyl)amino]-2-thiazolidineacetamide

1-(2-Aminoethyl)piperidine (0.27ml) was added to a stirred suspension of Intermediate 24 (500mg) in dichloromethane (20ml). The mixture was stirred for 24h then evaporated to a solid. The solid was triturated with ether then filtered. The

collected solid was crystallised from acetonitrile to afford the title compound as a white solid (362mg), mp 177-178°, $[\alpha]_D$ +79° (c 0.6, Me_2SO), ^1H nmr (DMSO-d_6) 1.13 (3H), 1.14 (3H), 1.38 (2H), 1.46 (10H), 2.30 (6H), 3.12 (6H), 3.40 (1H), 3.45 (1H), 3.50 (2H), 3.52 (2H), 3.79 (2H), 4.28 (2H), 4.32 (1H), 4.44 (1H), 4.84 (1H), 4.89 (1H), 7.78 (1H), 7.93 (2H), 8.25 (1H), 8.33 (1H) and 8.49 (1H).

Example 37

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimet 1-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[(4-(((1,1-dimethyl)ethoxy)carbonyl)phenyl)methyl]-α-[(2-phenyl-1-oxoethyl)amino]-2-thiazolidineacetamide

4-Aminomethylbenzoic acid 1,1-dimethylethylester acetic acid salt (279mg) and triethylamine (0.15ml) was added to a stirred suspension of Intermediate 24 (500mg) in dichloromethane (50ml). The mixture was stirred for 48h then diluted with dichloromethane, washed with water, 0.5N hydrochloric acid, saturated sodium bicarbonate solution, water and brine. The organic layer was dried, evaporated and the solid crystallised from acetronitrile to afford the title compound as a white solid (400mg), mp 158-159°, $[\alpha]_D$ +52° (c 0.5, Me_2SO), ^1H nmr (DMSO-d_6) 1.33 (6H), 1.38 (6H), 1.55 (9H), 3.18 (4H), 3.42 (2H), 3.51 (4H), 3.82 (2H), 4.29 (4H), 4.43 (2H), 4.89 (2H), 7.25 (15H), 7.31 (2H), 7.88 (2H), 7.96 (2H), 8.36 (2H), 8.50 (1H) and 8.61 (1H).

Example 38

[2R-[2α(R*),4]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[2-hydroxyethyl]-α-[(2-phenyl-1-oxoethyl)amino]-2-thiazolidineacetamide

Ethanolamine (0.11ml) was added to a stirred suspension of Intermediate 24 (500mg) in dichloromethane (50ml). The mixture was stirred for 24h then

evaporated to a solid. This was purified by column chromatography on silica gel (Merck Art 9385, 25g) using dichloromethane-ethanol (20:1 then 10:1) to afford a white solid (450mg). A portion was crystallised from acetone to give the title compound as white prisms, mp 147-148°, $[\alpha]_D$ +7.4° (c 0.8, Me_2SO), ^1H nmr (DMSO-d_6) 1.08 (3H), 1.23 (3H), 1.44 (3H), 1.46 (3H), 2.95-3.20 (8H), 3.40 (2H), 3.50 (4H), 3.78 (2H), 4.26 (2H), 4.40 (3H), 4.86 (2H), 7.25 (15H), 7.87 (1H), 8.09 (1H), 8.32 (1H) and 8.48 (1H).

Example 39

[2R-[2α(R*,Z),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(3-phenyl-1-oxo-2-propenyl)amino]-2-thiazolidineacetamide]]

A 10% solution of ethylamine in dichloromethane (0.75ml) was added to a stirred solution of Intermediate 25 (150mg) in dichloromethane (5ml). The mixture was stirred to 16h then evaporated to a solid. This was purified by column chromatography on silica gel (Merck Art 9385, 25g) using dichloromethane-methanol (15:1) to give a solid which was crystallised from acetone to afford the title compound as white prisms (30mg), mp 186-187°, $[\alpha]_D$ +106° (c 0.4, Me_2SO), ^1H nmr (DMSO-d_6) 1.00 (6H), 1.12 (6H), 1.50 (6H), 3.06 (4H), 3.18 (4H), 3.46 (2H), 3.79 (2H), 4.39 (2H), 4.83 (2H), 6.06 (2H), 6.63 (2H), 7.25 (3H), 7.65 (2H), 8.05 (4H) and 8.35 (2H).

Example 40

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[(4-carboxyphenyl)methyl]-α-[(2-phenyl-1-oxoethyl)amino]-2-thiazolidineacetamide

30% Hydrogen bromide in acetic acid (1ml) was added to a stirred solution of the product of Example 37 (433mg) in dichloromethane (20ml). The mixture was stirred for 10 min, then poured into saturated sodium bicarbonate. The suspension was filtered and the collected solid washed with water and dried. This was purified

by column chromatography on silica gel (Merck Art 9385, 25g) using ethyl acetate-ethanol-acetic acid (20:2:1) to afford the title compound as a white solid (90mg), mp 149-151° (softens), $[\alpha]_D$ +56° (c 0.6, Me_2SO), ^1H nmr (DMSO-d_6) 1.14 (6H), 1.50 (6H), 3.30 (6H), 3.85 (2H), 4.25 (4H), 4.44 (1H), 4.90 (2H), 7.25 (15H), 7.30 (2H), 8.37 (2H), 8.52 (1H) and 8.60 (1H).

Example 41

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[[(2-N,N-dimethylamino)phenyl]methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

2-N,N-dimethylaminobenzylamine (0.68g) was added to a stirred solution of Intermediate 1 (0.52g) in tetrahydrofuran (20ml). The solution was stirred for 22h. The resulting suspension was cooled in ice and filtered to afford the title compound as a white solid (300mg), which crystallised from acetronitrile to give white prisms, mp 204-206°, $[\alpha]_D$ +35° (c 1.04, MeOH), ^1H nmr (DMSO-d_6) 1.14 (6H), 1.50 (6H), 2.60 (12H), 3.15 (4H), 3.46 (2H), 3.51 (4H), 3.82 (2H), 4.20-4.50 (6H), 4.90 (2H), 6.89-7.31 (18H), 7.97 (2H) and 8.39 (4H).

Example 42

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[(4-hydroxymethyl)phenyl)methyl]-α-[(2-phenyl-1-oxoethyl)amino]-2-thiazolidineacetamide

4-Hydroxymethylbenzylamine (250mg) was added to a stirred suspension of Intermediate 24 (500mg) in dichloromethane (50ml). The mixture was stirred for 5 days then evaporated to a solid. This was purified by column chromatography on silica gel (Merck Art 9385, 50g) using dichloromethane-ethanol (20:1 then 15:1) to afford the title compound as a white solid (218mg), $[\alpha]_D$ +72° (c 0.6, Me_2SO), ^1H nmr (DMSO-d_6) 1.14 (6H), 1.50 (6H), 3.16 (4H), 3.43 (2H), 3.51 (4H), 3.82 (2H),

4.24 (4H), 4.45 (4H), 4.88 (2H), 5.11 (1H), 7.20 (19H), 7.94 (2H), 8.35 (2H) and 8.49 (2H).

Example 43

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[α-[[(2-hydroxyphenyl)acetyl]amino-5,5-dimethyl-N-(phenylmethyl)-2-thiazolidineacetamide]]

Benzylamine (0.19ml) was added to a stirred solution of Intermediate 26 (210mg) in tetrahydrofuran (15ml). The solution was stirred for 18h and more benzylamine (0.1ml) was added. Stirring was resumed for 1½h, after which the solution was partitioned between ethyl acetate and 0.2N-hydrochloric acid. The organic layer was washed sequentially with water, saturated sodium bicardonate solution, water and brine, dried and evaporated to give an off white solid (200mg). Crystallisation from ethyl acetate afforded the title compound as prisms (15mg), mp 155-160°, $[\alpha]_D$ +64° (c 0.39, MeOH), ^{1}H nmr (DMSO-d_6) 1.14 (6H), 1.49 (6H), 3.18 (4H), 3.40-3.51 (6H), 3.83 (2H), 4.28 (4H), 4.42 (2H), 4.89 (2H), 6.72 (4H), 7.08 (4H), 7.24 (10H), 7.99 (2H), 8.28 (2H), 8.52 (2H) and 9.67 (2H).

Example 44

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-[(4-(1-pyrrolidinyl)phenyl) methyl]-2-thiazolidineacetamide]]

4-(1-Pyrrolidinyl)benzylamine (0.89g) was added to a stirred soution of Intermediate 1 (0.58g) in dichloromethane (15ml). The solution was stirred for 24h, then concentrated and added dropwise to ether with rapid stirring. The resulting suspension was filtered to give a white solid (0.81g), which was crystallised from acetonitrile to afford the title compound as white prisms (360mg), mp 150-151°, $[\alpha]_D$ +61° (c 0.54, MeOH), ^{1}H nmr (DMSO-d_6) 1.12 (6H), 1.49 (6H), 1.92 (8H), 3.19 (12H), 3.41 (2H), 3.50 (4H), 3.81 (2H), 4.12 (4H), 4.41 (2H), 4.88 (2H), 6.42 (4H), 7.02 (4H), 7.28 (10H), 7.97 (2H) and 8.31 (4H).

Example 45

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[(N-hydroxymethylamino) carbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]]

To a solution of [2R-(2α(R*),4β)]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidine carboxylic acid (883mg) in anhydrous N,N-dimethylformamide (10ml) were added 1-hydroxybenzotriazole hydrate (337mg), dicyclohexylcarbodiimide (454mg) and N,N'-bis(2hydroxyethyl)- ethylenediamine (150mg). The mixture was stirred at 21° for 4h, a drop of glacial acetic acid was added and the solid was filtered off. The filtrate was partioned between ethyl acetate and water and the aqueous phase was re-extracted with ethyl acetate. The combined organic phases were washed sequentially with water, saturated aqueous sodium bicarbonate solution, water, 2N hydrochloric acid, water and saturated brine, dried and evaporated. The residue (522mg) was chromatographed on Silica Gel (50g; Merck 9385) eluting with chloroform-methanol (9:1). Appropriate fractions were combined and evaporated to give the title compound (88mg) as a foam, $[\alpha]_D$ +53.1° (c 0.60, MeOH) $[MH]^+$ observed 996.6, $[MH]^+$ expected 996.26.

Example 46

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetic acid, methyl ester]]

A suspension of Intermediate 1 (1.04g) in dry methanol (60ml) was stirred at 21^0. After ca. 45min a clear solution was obtained and after a further 2.25h the solution was evaporated to give a white foam which was triturated with isopropyl ether (10ml) to give the title compound as a white solid (1.01g). A portion of this material (494mg) was crystallised from ethyl acetate to afford white prisms, mp 114^0, $[\alpha]_D$ + 93.5^0 (c 1.07, $CHCl_3$).

Example 47

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

35%-Aqueous ammonia solution (0.5ml) was added to a stirred solution of Intermediate 1 (502mg) in tetrahydrofuran (25ml). The solution was stirred for 5.50h and additional ammonia solution (0.50ml) was added. Stirring was continued for a further 16h and the solution was then evaporated to dryness. The residue was crystallised from acetonitrile to provide the title compound (165mg), mp 179.5-181.5^0, $[\alpha]_D$ + 82^0 (c 1.0, MeOH).

Example 48

[2R-[2α(R*),4β]]-4,4'-1,2-[Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetic acid, phenylmethyl ester]]

A solution of Intermediate 1 (500mg) in phenylmethanol (10ml) was treated with triethylamine (0.10ml) and the solution was left for 48h then evaporated in vacuo. The residual oil was sequentially treated with light petroleum (bp40-60°), diethyl ether and diisopropyl ether to give a white solid. This was chromatographed on a column of silica gel (Merck 9385, 65g) using 5-10% acetone in ethyl acetate to give the title compound as a white foam (333mg) which was triturated with diisopropyl ether to afford a white solid (250mg), $[\alpha]_D$ +73^0 (c 1.04; $CHCl_3$).

Example 49

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(4-pyridinylmethyl)-2-thiazolidineacetamide]]

4-(Aminomethyl)pyridine (0.3ml) was added to a stirred solution of Intermediate 1 (505mg) in dichloromethane (25ml). The solution was stirred for 5 days and the deposited solid was collected by filtration, washed with dichloromethane and ether and dried (559mg). This material was crystallised twice from ethyl acetate to afford the title compound as white prisms (55mg), mp 148-149^0, $[\alpha]_D$ +15^0 (c 1.08, MeOH).

Example 50

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-(1-methylethyl)-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

Isopropylamine (0.25ml) was added to a stirred solution of Intermediate 1 (507mg) in dichloromethane (25ml). The solution was stirred for 7 days during which time a solid was deposited. This was collected by filtration, washed with dichloromethane and ether and dried (95mg). Crystallisation from acetonitrile afforded the title compound as white prisms (47mg), mp 191-191.5°, $[\alpha]_D$ +57° (c 0.66, MeOH).

Example 51

[2R-[2α(R*),4β]]-N,N'-[1,2-Ethanediylbis[5,5-dimethyl-2-[2-(1-morpholinyl)-2-oxo-1-[(phenylacetyl)amino]ethyl]-4-thiazolidinecarboxamide]]

Morpholine (0.26ml) was added to a stirred solution of Intermediate 1 (503mg) in dichloromethane (25ml). The solution was stirred for 4 days then evaporated to give a white solid (745mg). This was dissolved in the minimum of ethyl acetate and excess ether added to give a white precipitate which was collected, washed with ether and dried (576mg). Crystallisation from ethyl acetate - ether afforded the title compound as white prisms (321mg), mp 155^0, $[\alpha]_D$ $+62^0$ (c 0.965 MeOH).

Example 52

[2R-[2α(R^*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetic acid, hydrazide]]

A solution of hydrazine hydrate (0.21ml) was added to a stirred solution of Intermediate 1 (501mg) in dichloromethane (25ml). The reaction mixture was stirred for 5h. The precipitated solid was collected by filtration, washed with dichloromethane and ether and dried (495mg). Crystallisation from acetonitrile

afforded the title compound as white prisms (225mg), mp 158°, $[\alpha]_D$ +58° (c 1.13, MeOH).

Example 53

[2R-[2α(R*),4β]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-hydroxy-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

A solution of hydroxylamine hydrochloride (200mg) and triethylamine (0.40ml) in dichloromethane (30ml) was added to a stirred solution of intermediate 1 (502mg) in dichloromethane (20ml) at -35° under an atmosphere of nitrogen. The reaction mixture was allowed to warm to +21° and stirred for 21h. The precipitated solid was collected, washed with dichloromethane and dried (150mg). Crystallisation from acetonitrile afforded the title compound as white prisms (69mg), m.p. 161, $[\alpha]_D$ +65° (c 0.89, MeOH). Upon standing the liquors deposited a second crop of similar crystalline material (15mg).

Example 54

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-N-Ethyl-5,5-dimethyl-4-[N-[2-[[(5,5-dimethyl-2-[[(phenylacetyl)amino]methyl]-4-thiazolidinyl) carbonyl]amino]ethyl]-α-[(phenylacetyl)amino]-2-thiazoldineacetamide]

1-Hydroxybenzotriazole hydrate (1.23g), N,N'-dicyclohexylcarbodiimide (1.80g) and ethylenediamine (0.27ml) were successively added to a stirred solution of Intermediate 27 (1.52g) and [2R-[2α,4α]]-5,5-dimethyl-2-[[(phenylacetyl)amino]methyl]-4-thiazolidinecarboxylic acid (1.23g) in anhydrous tetrahydrofuran (30ml). The solution was stirred for 1.5h during which time a solid precipitated. Acetic acid (2 drops) was added and the mixture filtered with the aid of tetrahydrofuran (10ml). The filtrate was diluted with ethyl acetate (200ml) and sequentially washed with saturated sodium bicarbonate, water and brine solution, then dried and evaporated to dryness. The residue (2.4g) was subjected to flash chromatography on silica gel (Merck 9385, 300g) using 5-10% ethanol in ethyl

acetate to give the title compound as a white solid (437mg) which crystallised from acetonitrile as white prisms (292mg), mp 121 - 122°, $[\alpha]_D$ + 78° (c 1.06; MeOH).

Example 55

[2S-[2α(S*),4β]]and[2R-[2α(R*),4β]2'S-[2'α(S*),4'β]]-4,4'-(1,2-Ethanediyl) bis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]

A solution of the product of Example 1 (500mg) in trifluoroacetic acid (3.5ml) was stirred for 100 min then evaporated in vacuo. The residue was dissolved in methanol, neutralised with sodium bicarbonate and filtered. The filtrate was evaporated and the residual gum treated with acetonitrile to give a white solid (100mg). A portion of this material (25mg) was subjected to purification by preparative HPLC (ODS - 2 column using 40% acetonitrile in water) to give three components. The component with lowest retention time had identical HPLC mobility to starting material and was not pursued. The component with intermediate retention time (8mg) proved to be the asymmetric title compound isomer, m.p. 224-225°; whilst the component with longest retention time (5mg) was the symmetric title compound isomer, m.p. 220-223°.

Example 56

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-N-Ethyl-5,5-dimethyl-4-[N-[2-[[[(5,5-dimethyl-2-[1-[(phenylcarbonyl)amino]-2-oxo-2-(ethylamino)ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]-α-[(phenylacetyl)amino]-2-thiazoldineacetamide]

Ethyl chloroformate (1.15ml) was added dropwise to a stirred solution of 6-benzamidopenicillanic acid (1.93g) and benzylpenicillin N-ethylpiperidine salt (2.69g) in dry dichloromethane (80ml) containing N-ethylpiperidine (0.83ml) at -10° under an atmosphere of nitrogen. The mixture was stirred at -10° for 1.5h and ethylenediamine (1.20ml) was added. The resulting suspension was stirred for 2h at +21° then water (100ml) was added and the layers separated. The aqueous layer

was further extracted with dichloromethane (40ml) and the combined organic portions were washed sequentially with water, saturated sodium bicarbonate water, 0.5N-hydrochloric acid, water and saturated brine solution. The dried solution was treated with ethylamine (6ml) and set aside for 24h then evaporated to a yellow solid (3.6g). A portion of this was purified by flash chromatography on silica gel (Merck 9385; 300g) using ethyl acetate - ethanol (19:1) to give the title compound as a white solid (342mg) which crystallised from acetonitrile as white prisms (200mg), mp. 149-151°, $[\alpha]_D$ + 12° (c 1.0; MeOH).

Example 57

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[α-[[(cyclohexyl)acetyl]amino]-5,5-dimethyl-N-(phenylmethyl)-2-thiazolidineacetamide]]

Cyclohexylacetic acid (134mg) and 1 - (3 - dimethylaminopropyl) - 3 - ethylcarbodiimide hydrochloride (189mg) were added to a stirred solution of Intermediate 9 (300 mg) in dichloromethane (25ml). The mixture was stirred for 4h and the precipitated solid was collected by filtration, washed with dichloromethane and ether and dried to give the title compound as a cystalline white solid (134mg). A portion of this material was recrystallised from acetonitrile to afford an analytical sample, mp. 176-177°.

Example 58

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[α-[[(2-chlorophenyl-5-methyl-3-phenyl-4-isoxazolyl)carbonyl]amino]-5,5-dimethyl-N-(2-pyridinylmethyl)-2-thiazolidineacetamide]]

2-Pyridylmethylamine (1.2ml) was added to a stirred solution of Intermediate 36 (300mg) in dichloromethane (15ml). The solution was stirred for 30h and the deposited solid collected by filtration, washed with dichloromethane and dried to give the title compound as white prisms (210mg), m.p. 145-147°, $[\alpha]_D$ + 47° (c 0.76; Me_2SO).

Example 59

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-carboxymethyl-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

30%-Hydrogen bromide in acetic acid (1.0ml) was added to a stirred solution of the product of Example 13 (209mg) in dichloromethane (10ml). The reaction mixture was stirred for 10min then poured into saturated sodium bicarbonate (20ml) - dichloromethane (10ml) and the layers separated. The aqueous portion was acidified to pH2 with 2 N-hydrochloric acid and extracted with ethyl acetate. The extract was dried and evaporated to a white solid (167mg) which was purified on a column of silica gel (Merck Art 9385, 20g) using chloroform - methanol - acetic acid (22:4:1) as eluant. Appropriate fractions were combined to give the title compound as a white solid (118mg), m.p. 225-230° (dec.), $[\alpha]_D$ + 72° (c 0.92; H_2O).

Example 60

[2R-[2α(R*),4β]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-(2-(4-imidazolyl)ethyl-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

Histamine (0.32g) was added to a stirred solution of Intermediate 1 (0.50g) in dry dichloromethane (20ml). The mixture was stirred under an atmosphere of nitrogen for 22h then evaporated to dryness. The residue was triturated several times with water which was decanted then it was dissolved in methanol and evaporated to give a white solid (0.63g). A portion of this (0.44g) was crystallised from acetonitrile to afford the title compound (0.20g) as hygroscopic white prisms, mp 148-151°, $[\alpha]_D$ +74° (c 0.93; Me_2SO).

Example 61

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[α-[(4-fluoro)phenylacetyl)amino]-5,5-dimethyl-N-((2-pyridinyl)methyl)-2-thiazolidineacetamide]]

4-fluorophenylacetic acid (190mg) and 1-(3-Dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (280mg) were added to a solution of Intermediate 11 (300mg) in dichloromethane (20ml). The reaction solution was stirred for 3h, then washed sequentially with water, saturated sodium bicarbonate solution and brine, dried and evaporated (375mg). The resulting cream solid was purified by column chromatography on silica gel (Merck Art 9385; 37g), eluting with 10-20% ethanol in ethyl acetate to afford the title compound (60mg). Crystallisation from acetonitrile gave white prisms (30mg), mp 137-138°, $[\alpha]_D$ +98° (c 0.15, MeOH).

Example 62

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-[2-(1-pyrrolidinyl)ethyl]-2-thiazolidineacetamide]]

N-(2-Aminoethyl)pyrrolidine (0.37ml) was added to a stirred solution of Intermediate 1 (0.50g) in dry dichloromethane (20ml). The mixture was stirred for 24h under an atmosphere of nitrogen then evaporated to dryness. The residue was stirred with ether and the insoluble white solid was collected by filtration (615mg). Crystallisation from acetonitrile (20ml) afforded the title compound (255mg) as hygroscopic white prisms, mp 171.5-173.5°, $[\alpha]_D$ +74° (c 0.78, Me_2SO).

Example 63

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-[2-(4-morpholinyl)ethyl]-2-thiazolidineacetamide]]

4-(2-Aminoethyl)morpholine (0.38ml) was added to a stirred solution of Intermediate 1 (0.50g) in dry dichloromethane (20ml). The mixture was stirred for 16h under an atmosphere of nitrogen then evaporated to give a gummy white solid (0.70g). This was crystallised from acetonitrile to give hygroscopic white prisms (310mg). Recrystallisation from acetone afforded the title compound (195mg) as hygroscopic white prisms, mp 180-182°, $[\alpha]_D$ +65° (c 1.00, Me_2SO).

Example 64

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(((2-phenylmethyl)phenyl)carbonyl)amino]-2-thiazolidineacetamide]]

Ethylamine (0.05ml) was added to a solution of Intermediate 28 (100mg) in dichloromethane (5ml). After 7h the solvent was evaporated and the residue was triturated with ether to give the title compound as a solid (85mg), mp 176-177° $[\alpha]_D$ +60° (c = 0.58, Me_2SO).

Example 65

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[(4-(aminomethyl)phenyl)methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

4-(Aminomethyl)benzylamine (1g) was added to a solution of Intermediate 1 (0.5G) in dichloromethane (50ml). After 20h the solution was concentrated to ca 10ml. Ether was added to complete the precipitation of a solid which was collected by filtration. Crystallisation from acetonitrile afforded the title compound as white prisms (0.125g), mp 160.5-162°, $[\alpha]_D$ +64° (c 0.64, Me_2SO).

Example 66

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-(4-carboxyphenyl)methyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]

A solution of 30% hydrogen bromide in acetic acid (2.5ml) was added to a stirred solution of Intermediate 29 (500mg) in dichloromethane (25ml). The reaction solution was stirred for 5 min, after which it was poured into saturated sodium bicarbonate solution (75ml). The suspension was filtered to give the title compound, mp 170-171°, $[\alpha]_D$ +56° (c 0.22, MeOH).

Example 67

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(3-thienylacetyl)amino]-2-thiazolidineacetamide]]

A 10% solution of ethylamine in dichloromethane (0.75ml) was added to a solution of Intermediate 35 (150mg) in dichloromethane (5ml). The solution was allowed to stand for 20h, then evaporated to a solid, which crystallised from acetonitrile to give the title compound as white prisms (36mg), mp 168-169°, $[\alpha]_D$ +86° (c 0.4, Me_2SO).

Example 68

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-2-((4-aminophenyl)ethyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

2-(4-Aminophenyl)ethylamine (610mg) was added to a stirred solution of Intermediate 1 (500mg) in dichloromethane (20ml). The reaction solution was stirred for 24h. The resulting suspension was filtered, and the gum triturated with ether to afford the title compound as a white solid. Crystallisation from acetonitrile yielded white prisms, mp 174-176°, $[\alpha]_D$ +38° (c 0.92, MeOH).

Example 69

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-(4-(hydroxymethyl)phenyl)methyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

A solution of Intermediate 1 (1.05g) and 4-hydroxymethylbenzylamine (1.23g) in tetrahydrofuran (80ml) was stirred at ca 21° for 42h. The solution was concentrated to low volume and ethyl acetate and water were added. The organic phase was washed sequentially with 2N hydrochloric acid, water, saturated aqueous sodium bicarbonate solution, water and saturated brine, dried and concentrated to ca 15ml. The solid (922mg) which had precipitated was filtered off and chromatographed on silica gel (100g; Merck 9385) eluting with 19:1 and then 9:1 mixtures of chloroform and methanol. Appropriate fractions were combined and evaporated and the resulting solid (424mg) was crystallised from acetonitrile (10ml)

to give the title compound (236mg) as prisms, mp 171°, $[\alpha]_D$ +38.8° (c 0.95, MeOH).

Example 70

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(2-pyridinylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]]

2-Pyridinylacetic acid hydrochloride (181mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (400mg) and a solution of triethylamine (0.15ml) in dioxan (10ml) were added to a stirred solution of Intermediate 4 (350mg) in dioxan (30ml)-water (5ml). The mixture was stirred for 5h and additional 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (200mg) was added. The mixture was stirred for a further 19h then evaporated to dryness and the residue partitioned between ethyl acetate and saturated sodium bicarbonate. The organic layer was separated and the organic portion washed with further sodium bicarbonate, dried and evaporated. The residue was purified by chromatography on a column of silica gel (Merck Art 9385, 50g) using chloroform methanol (9:1) as eluant to give a pale yellow solid (240mg) which crystallised from acetonitrile to give the title compound as white prisms (150mg), m.p. 132-134^0, $[\alpha]_D$ +70 (c 1.0; MeOH).

Example 71

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetic acid, 2-phenylhydrazide]]

Freshly distilled phenylhydrazine (0.43ml) was added to a stirred solution of Intermediate 1 (500mg) in dichloromethane (25ml). The mixture was stirred for 3 days and the deposited solid was collected and dried (407mg). This material was purified on a column of silica gel (Merck Art 9385, 20g) using chloroform-methanol (19:1). Appropriate fractions were combined and evaporated to give the title compound as a pale yellow solid (177mg), $[\alpha]_D$ +45^0 (c 1.03; MeOH).

Example 72

[2R-[2α(R*),4β]]-N,N'-[1,2-Ethanediylbis[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-(4-phenyl-1-piperazinyl)ethyl]-4-thiazolidinecarboxamide]]

N-Phenylpiperazine (0.66ml) was added to a stirred solution of Intermediate 1 (502mg) in dry dichloromethane (25ml). The solution was stirred for 5 days then evaporated to give a white foam. This was stirred with ether to give a white solid which was collected and dried (767mg). This material was crystallised twice from acetonitrile to give white prisms (393mg). A portion of this material (100mg) was further purified by preparative HPLC using acetonitrile-water (7:3) as eluant on a S5-ODS-2 column to give the title compound as a white solid (45mg), m.p. 154-157^0, $[\alpha]_D$ +82^0 (c 0.55; MeOH).

Example 73

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[(1-naphthalenyl)methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

1-Naphthalenemethylamine (0.43ml) was added to a stirred solution of Intermediate 1 (502mg) in dry dichloromethane (25ml). The solution was stirred under an atmosphere of nitrogen for 2 days during which time a solid precipitated. This was collected and dried (285mg) and crystallised from acetonitrile to furnish the title compound as white prisms (129mg), m.p. 176-178^0, $[\alpha]_D$ +30^0 (c 0.92; MeOH).

Example 74

[2R-[2α(R*),4β(R*S*)],2'R-[2'α(R*),4'β]]-4,4'-[(1-Methyl-1,2-ethanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl) amino]-N-(phenylmethyl)-2-thiazolidineacetamide]

Benzylamine (0.54ml) was added to a stirred solution of Intermediate 30 (572mg) in dichloromethane (10ml). The solution was stirred for 3 days and a white solid was then filtered off and washed with ether. Crystallisation from acetonitrile gave the title compound as a white powder, mp 177-179°, $[\alpha]_D$ + 67° (c 1.07, in MeOH) ^{1}H nmr (DMSO-d_6) δ 1.15 (3H), 1.25 (6H), 1.62 (6H), 3.10 - 3.40 (2H),

3.50 - 3.60 (2H), 3.62 (4H), 3.90 - 4.10 (3H), 4.40 (4H), 4.50 - 4.60 (2H), 4.95 - 5.08 (2H), 7.25 - 7.45 (20H), 7.90 (1H), 7.98 - 8.10 (1H), 8.50 (2H), 8.55 - 8.70 (2H).

Example 75

[2R-[2α(R*),4β(R*)],2'R-[2'α(R*),4'β]]-4,4'-[(1-Methyl-1,2-ethanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]

1-Hydroxybenzotriazole monohydrate (190mg) and R-(-)-1,2-diaminopropane (53μl) were added successively to a stirred solution of [2R-(2α(R*),4β]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidine carboxylic acid (500mg) in tetrahydrofuran (8ml). After 15 min N,N-dicyclohexylcarbodiimide (256mg) was added and the mixture stirred for 2h. The reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel (Merck 9385, 30g) eluting with chloroform : methanol mixtures varying from 50:1 to 15:1 to give a mixture of three components. Further purification was achieved by crystallisation from acetonitrile, and by silica gel chromatography (Merck 9385, 10g) eluting with ethyl acetate : cyclohexane mixtures 4:1 to 8:1 and ethyl acetate : ethanol mixtures 12:1 to 8:1. Crystallisation from hot acetonitrile gave the title compound as white crystals, mp 199 - 201°, $[\alpha]_D$ + 59° (c 1.03, MeOH), ^{1}H nmr (DMSO-d_6) δ 1.05 (3H), 1.15 (6H), 1.50 (6H), 3.0 - 3.25 (2H), 3.39 - 3.45 (2H), 3.50 (4H), 3.75 - 3.95 (3H), 4.25 (4H), 4.43 (2H), 4.90 (2H), 7.15 - 7.32 (20H), 7.78 (1H), 7.9 (1H), 8.36 (2H) and 8.50 (2H).

Example 76

[2R-[2α(R*),4β(R*,S*)],2'R-[2'α(R*),4'β]]-4,4'-[(1-Hydroxymethyl-1,2-ethanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]

To a solution of [2R-(2α(R*),4β]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidine carboxylic acid (541mg), 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluorborate

(393mg), and Intermediate 31 (100mg) in dry N,N-dimethylformamide (5ml) was added N,N-diisopropylethylamine (426μl) and the resulting solution stirred at 21°C under nitrogen for 18h. The reaction mixture was partitioned between ethylacetate and 10% aqueous citric acid and the organic phase washed with brine, dried and evaporated. The resulting solid was chromatographed on silica gel (Merck 7734, 20g), eluting with chloroform-methanol (20:1) which gave a mixture of components. Further purification was achieved by silica gel chromatography (Merck 7734, 20g) eluting with chloroform-methanol 40:1 to 20:1. Crystallisation from ethylacetate gave the title compound as a white solid mp 130-133°, $[\alpha]_D$ +62° (c 1.15, $CHCl_3$), ^1H nmr (DMSO-d_6) δ 1.10 (6H), 1.46 (6H), 3.10-3.45 (4H), 3.46 (4H), 3.80 (3H), 4.10-4.50 (6H), 4.70 (1H), 4.85 (2H), 7.16 (20H), 7.61 (1H), 7.82 (1H), 8.28 (2H) and 8.45 (2H).

Example 77

[2R-[2α(R*),4β]]-4,4'-[(1,1-Dimethyl-1,2-ethanediyl)bis (aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]

To a stirred solution of [2R-(2α(R*),4β)]-5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidine carboxylic acid (500mg) in dimethylformamide (10ml) was added 1-hydroxybenzotriazole (190mg). After 10 min 1,2-diamino-2-methylpropane (55mg) was added, followed by dicyclobexylcarbodiimide (256mg) after a further 10 min. The mixture was stirred for 4h and then filtered. The filtrate was partitioned between ethyl acetate and water and the organic extract washed with 2N hydrochloric acid, sodium bicarbonate solution and brine. The organic extract was dried and evaporated to leave a solid residue which was purified by silica gel chromatography using chloroform-methanol mixtures (50:1, 40:1, 30:1) as eluant. Further column chromatography using ethyl acetate-ethanol (40:1) gave the title compound as a white solid, mp 116-118°, $[\alpha]_D$ +62° (c 1.03 MeOH), ^1Hnmr (DMSO-d_6) δ 8.45-8.60 (2H), 8.42-8.43 (2H), 7.98 (1H), 7.56 (1H), 7.15-7.35 (20H), 4.85-4.95 (2H), 4.15-4.5 (6H), 3.82-3.95 (1H), 3.7-3.82 (1H) and 3.15-3.25 (1H).

Example 78

[2R-[2α(R*),4β(R*,S*)],2'R-[2'α(R*),4'β]]-4,4'-[(1-Carboxy-1,2-ethanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]

A mixture of 10%-palladium on charcoal (130mg) and Intermediate 38 (263mg) in methanol (10ml) was stirred under an atmosphere of hydrogen for 24h when additional catalyst (100mg) was added. The mixture was stirred under hydrogen for an additional 48h, then filtered and the filtrate evaporated. The residue was re-dissolved in methanol (10ml) and 10%-Palladium on charcoal (150mg) added. The mixture was stirred under a hydrogen atmosphere for a further 72h. The catalyst was removed by filtration and the filtrate evaporated. The residue was purified by chromatography on silica gel (Merck 7734, 3g) eluting with chloroform then chloroform-methanol (10:1) to give the title compound as a white solid (41mg) mp 173-178°, $[\alpha]_D$ +96° (c 0.94, MeOH), ^{1}H nmr (DMSO-d_6) δ 1.15 (6H), 1.50 (6H), 3.50 (4H), 3.70-4.00 (3H), 4.25 (4H), 4.42 (2H), 4.88 (2H), 7.25 (20H), 7.63 (1H), 8.38 (2H) and 8.54 (2H).

Example 79

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[2-(1,1-dimethylethoxy)-2-oxoethyl]-α-[[[(1,1'-biphenyl)-2-yl]carbonyl]amino]-2-thiazolidineacetamide]]

A solution of Intermediate 40 (500g) in dichloromethane (20ml) containing triethylamine (0.42ml) was treated with glycine t-butyl ester hydrochloride (500mg). After eleven days the solution was washed with water and saturated brine then dried and evaporated to give a gum which was chromatographed on silica gel (Merck Art 9385, 50g) using chloroform-methanol (19:1). Appropriate fractions were combined and evaporated to give the title compound as a white solid (248mg), $[\alpha]_D$ +42.7° (c 0.37; Me_2SO), ^{1}H nmr (DMSO-d_6 δ 1.16 (6H), 1.42 (18H), 1.51 (6H), 3.26 (4H),

3.44 (2H), 3.72 (4H), 3.83 (2H), 4.49 (2H), 4.94 (2H), 7.2-7.6 (18H), 8.08 (2H), 8.18 (2H) and 8.71 (2H).

Example 80

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[[(4-dimethylamino)phenyl]methyl]-α-[[[(1,1'-biphenyl-2-yl]carbonyl]amino]-2-thiazolidineacetamide]]

A solution of Intermediate 40 (300mg) in dichloromethane (30ml) containing triethylamine (0.51ml) was treated with 4-(dimethylamino)benzylamine dihydrochloride (408mg). After six days the solvent was evaporated and the residue was chromatographed on silica gel (Merck Art 9385, 5g) using chloroform-methanol (19:1). Appropriate fractions were combined and evaporated to give a white solid. A portion (160mg) was further purified by preparative HPLC (S5-ODS-2 column using aqueous acetonitrile) to give the title compound (83mg), $[\alpha]_D$ +45.1° (c 0.49; Me_2SO), ^1H nmr (DMSO-d_6) δ 1.17 (6H), 1.52 (6H), 2.86 (12H), 3.43 (2H), 3.85 (2H), 4.16 (4H), 4.45 (2H), 4.96 (2H), 6.66 (4H), 4.45 (2H), 4.96 (2H), 6.66 (4H), 7.10 (4H), 7.2-7.55 (18H), 8.1-8.25 (4H) and 8.64 (2H).

Example 81

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[[4-(2-hydroxyethyl)phenyl]methyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

To a stirred suspension of 4-(2-hydroxyethyl)benzylamine hydrochloride (1.13g) in acetonitrile (110ml) was added triethylamine (0.84ml). After 40 min, Intermediate 1 (693mg) was added and the mixture was stirred at 21° for 3 days with more acetonitrile (200ml) being added after the first day. The solution was evaporated to dryness and the residue was partitioned between ethyl acetate and water. The organic phase was washed sequentially with 2N-hydrochloric acid, water, saturated sodium bicarbonate solution, water and saturated brine, then dried and evaporated to dryness. Flash chromatography on silica gel (Merck Art 9385g,

70g) eluting with chloroform-methanol (19:1) (800ml) gave fractions which were combined as appropriate and evaporated to give a product which was crystallised from acetonitrile to give the title compound (77mg), mp 152°, $[\alpha]_D$ +43.7° (c 0.86; MeOH). Other fractions were combined and evaporated to give [2S-[2α,5α,6β]2'R-[2'α(R*)4β]]-3,3-dimethyl-2-[[[[2-[[[[(2-hydroxyethyl)phenyl]methyl]amino]ethyl]-2-oxo-1-[(phenylacetyl)amino]-4-thiazolidinyl]carbonyl]amino]ethyl]-7-oxo-6-[(phenylacetyl)amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxamide as a white solid (194mg), m.p. 120-121°, $[\alpha]_D$ +155° (c 0.98; MeOH).

Example 82

[2R-[2α(R*,S*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[[1-hydroxymethyl-2-phenyl]ethyl]-5,5-dimethyl-α-[(phenyacetyl)amino]-2-thiazolidineacetamide]]

A solution of Intermediate 1 (693mg) and (S)-(-)-2-amino-3-phenylpropanol (1.046g) in dichloromethane (35ml) was stirred at 21° for 18h. More dichloromethane (50ml) was added and the solution was washed sequentially with 2N-hydrochloric acid, water, saturated aqueous sodium bicarbonate, water and brine solution then dried and evaporated to give a solid which was crystallised three times from ethyl acetate to give the title compound (94mg), m.p. 125-127°, $[\alpha]_D$ +36.1° (c 0.873; MeOH).

Example 83

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[[4-(diethylamino)phenyl]methyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

4-(Diethylamino)benzylamine (780mg) and triethylamine(0.2ml) were added to a stirred solution of Intermediate 1 (505mg) in dioxan (25ml) and N,N-dimethylformamide (15ml) and the mixture was stirred for 113h. Further 4-(diethylamino)benzylamine (320mg) and triethylamine (0.6ml) were added and stirring was continued for a further 18h. The mixture was partitioned between water

and ethyl acetate and the organic portion was washed with water and saturated brine then evaporated to dryness. The residue was crystallised twice from acetonitrile to give the title compound (310mg), m.p. 159-161°, $[\alpha]_D$ +54.7° (c 0.415; MeOH), ^{1}H nmr (DMSO-d_6) δ 1.05 (6H), 1.14 (6H), 1.48 (6H), 3.16 (4H), 3.30 (4H), 3.42 (2H), 3.51 (4H), 3.82 (2H), 4.11 (4H), 4.20 (2H), 4.88 (2H), 6.54 + 6.99 (4H), 7.25 (18H), 7.98 (2H) and 8.32 (2H).

Example 84

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[(4-nitrophenyl)methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

To a stirred solution of Intermediate 1 (500mg) in dichloromethane (20ml) were added 4-nitrobenzylamine hydrochloride (830mg) and triethylamine (0.6ml). The suspension was stirred at ca 21° for 111h, more dichloromethane (40ml) was added and the solution was washed sequentially with water, 0.5N-hydrochloric acid, water, saturated aqueous sodium bicarbonate and saturated brine solution, then dried and evaporated to give a foam. This was triturated with ether to give a solid which was crystallised twice from acetonitrile to give the title compound (200mg), m.p. 160-161°, $[\alpha]_D$ +112° (c 0.577; MeOH), ^{1}H nmr (DMSO-d_6) δ 1.15 (6H), 1.50 (6H), 3.17 (4H), 3.43 (2H), 3.53 (4H), 3.88 (2H), 4.40 (6H), 4.90 (2H), 7.28 (10H), 7.49 + 8.11 (8H), 8.02 (2H), 8.43 (2H) and 8.74 (2H).

Example 85

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[[4-aminosulphonyl)phenyl]methyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

To a stirred solution of Intermediate 1 (500mg) in N,N-dimethylformamide (20ml) were added triethylamine (0.6ml) and 4-aminomethylbenzenesulphonamide hydrochloride (975mg). The resulting suspension was stirred at 21° for 48h and then the solid was filtered off and the filtrate was partitioned between ethyl acetate (200ml), ethanol (6ml) and water (50ml). The organic phase was washed

sequentially with 2N-hydrochloric acid, water, saturated aqueous sodium bicarbonate, water and saturated brine solution then evaporated to give a solid which was crystallised from isopropanol (100ml) to give the title compound (160mg), m.p. 182-183°, $[\alpha]_D$ +42.1° (c 0.98; Me_2SO).

Example 86

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-[[4-aminocarbonyl)phenyl]methyl]-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

To a stirred solution of Intermediate 1 (500mg) in dichloromethane (20ml) was added 4-aminomethylbenzamide (650mg). The resulting suspension was stirred at 21° for 60h when N,N-dimethylformamide (5ml) was added to give a solution which was stirred at 21° for 24h. The resulting solid was filtered off and washed in turn with dichloromethane, ether, methanol and ether to give the title compound (390mg), m.p. 158-159°, $[\alpha]_D$ +46.2° (c 1.125; Me_2SO).

Example 87

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-methyl-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]]

A solution of Intermediate 1 (1.0g) in a saturated solution of methylamine in dichloromethane (80ml) was stirred at 21° for 108h. Triethylamine (0.5ml) was added and stirring continued for a further 3h. The resulting solid was filtered off, the filtrate was stirred for 72h, washed with water and saturated brine, dried and evaporated to give a solid. The solids were combined and chromatographed on silica gel (Merck Art 9385) eluting with chloroform containing ethanol (10-20%). Appropriate fractions were combined and evaporated to give a solid which was crystallised from acetonitrile to give the title compound (43mg), m.p. 185-186°, $[\alpha]_D$ +41° (c 0.48; MeOH).

Example 88

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[[[2-(dimethylamino)phenyl]carbonyl]amino]-N-(phenylmethyl)-2-thiazolidineacetamide]]

A solution of Intermediate 9 (900mg), 2-dimethylaminobenzoic acid (625mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (550mg) in dioxan (15ml) - water (15ml) was stirred at 21° for 141h. Additional portions of the acid (250mg) and the carbodiimide reagent (250mg) were added after 18h, 95h and 117h. The solution was extracted with ethyl acetate and the extract sequentially with water, saturated aqueous sodium bicarbonate and brine solution, then dried and evaporated to give a foam. Flash chromatography on silica gel (Merck 9385; 85g) eluting with 2% methanol in chloroform gave the title compound (110mg) which was crystallised from acetonitrile to give the title compound as a white solid (15mg), m.p. 250° dec, ^{1}H nmr (DMSO-d_6) δ 1.13 (6H), 1.49 (6H), 2.66 (12H), 3.16 (4H), 3.44 (2H), 4.00 (2H), 4.29 (4H), 4.53 (2H), 4.92 (2H), 7.1-7.8 (18H), 8.07 (2H), 8.64 (2H) and 9.94 (2H).

Example 89

[2R-[2α(R*),4β]2'R-[2α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-[[[(4-dimethylamino)phenyl]methyl]amino]-2-oxo-1-[(phenylacetyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[2-N,N-dimethylamino)ethyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

2-(Dimethylamino)ethylamine (0.2ml) was added to a stirred solution of Intermediate 42 (500mg) in dichloromethane (50ml). The reaction solution was stirred for 24h and then evaporated. The residue was triturated with diethyl ether and the resulting solid was chromatographed on silica gel (Merck Art 9385, 50g) eluting with dichloromethane-ethanol-triethamine (20:2:1). Appropriate fractions were combined to give a solid that crystallised from ethyl acetate to give the title compound as white prisms (275mg), m.p. 121-123°, $[\alpha]_D$ +66° (c 0.6; Me_2CO).

Example 90

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetic acid, 4-(nitrophenyl)methyl ester

Triethylamine (0.28ml) and 4-nitrobenzyl alcohol(1.73g) were added to a stirred solution of Intermediate 24 (1.5g) in dichloromethane (150ml). The reaction solution was stirred for 7 days and then evaporated. The residue was triturated with ether and the resulting solid was chromatographed on silica gel (Merck Art 9385, 80g) eluting with ethyl acetate-acetone (3:1). Appropriate fractions were combined to give the title compound (890mg). Two recrystallisations from ethyl acetate gave the title compound as white prisms (677mg), m.p. 123-125°, $[\alpha]_D$ +62° (c 0.6, Me_2SO), ^1H nmr (DMSO-d_6) δ 1.15 (6H), 1.45 (6H), 3.15 (4H), 3.50 (6H), 3.80 (1H), 4.00 (1H), 4.25 (2H), 4.45 (2H), 4.90 (1H), 5.00 (1H), 5.30 (2H), 7.30 (15H), 7.60 (2H), 7.95 (1H), 8.05 (1H), 8.20 (2H), 8.35 (1H), 8.55 (1H) and 8.65 (1H).

Example 91

[2R-[2α(R*),4β]2'R-[2'α(R*),4β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[2-(1,1'-dimethylethoxy)-2-oxoethyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

Glycine t-butyl ester hydrochloride (840mg) and triethylamine (0.68ml) were added to a stirred solution of Intermediate 24 (1.0g) in dichloromethane (100ml). The reactions solution was stirred for 14 days, then washed sequentially with 0.5N-hydrochloric acid, water and brine and dried and evaporated. The resulting solid was chromatographed on silica gel (Merck Art 9385, 100g) eluting with ethyl acetate-acetone (3:1). Appropriate fractions were combined to give the title compound (850mg) as a white foam, $[\alpha]_D$ +75° (c 0.5; Me_2SO).

Example 92

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[[4-(dimethylamino)phenyl]methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

4-(Dimethylamino)benzylamine dihydrochloride (1.14g) and triethylamine (1.5ml) were added to a stirred solution of Intermediate 24 (680mg) in dichloromethane (50ml). The reaction was stirred for 4 days, then washed sequentially with water and brine, dried and evaporated. The resulting solid was purified by column chromatography on silica gel (Merck Art 9385; 30g), eluting with ethyl acetate-acetone (3:2). Appropriate fractions were combined to give the title compound (500mg). Recrystallisation from acetontrile afforded the title compound (250mg) as white prisms, m.p. 157-159°, $[\alpha]_D$ +43° (c 0.6; Me_2SO), ^1H nmr (DMSO-d_6)_δ 1.15 (6H), 1.50 (6H), 2.85 (6H), 3.20 (4H), 3.45 (2H), 3.50 (4H), 3.70 (2H), 4.20 (4H), 4.40 (2H), 4.90 (2H), 6.60 (2H), 7.05 (2H), 7.25 (15H), 7.95 (2H), 8.35 (3H) and 8.5 (1H).

Example 93

[2R-[2α(R*),4β]2'R-[2'α(R*),4β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-(phenylmethyl)-α-[[(phenylmethoxy)carbonyl]amino]-2-thiazolidineacetamide

Benzylamine (1ml) was added to a stirred solution of Intermediate 19 (1.30g) in dichloromethane (50ml). The reaction solution was stirred for 3 days and then evaporated. The residue was chromatographed on silica gel (Merck Art 9385, 30g) eluting with dichloromethane-ethanol (20:1). The appropriate fractions were combined to afford the title compound (780mg), mp 111-113°, $[\alpha]_D$ +133° (c 0.7; Me_2SO).

Example 94

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-Dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-(phenylmethyl)-α-(acetylamino)-2-thiazolidineacetamide

A solution of hydrogen bromide in acetic acid (45% w/v; 4.3ml) in dichloromethane (25ml) was added to a stirred solution of Example 93 (780mg) in dichloromethane (25ml). The reaction solution was stirred for 40 minutes and then poured into saturated aqueous sodium bicarbonate (500ml). The mixture was stirred for 20 minutes and then the phases were separated. The aqueous phase was extracted with dichloromethane and the organic extract was washed with brine, dried and evaporated. The resulting solid was chromatographed on silica gel (Merck Art 9385, 50g) eluting with dichloromethane-ethanol (20:1). Appropriate fractions were combined to afford the title compound (108mg), m.p. 137-139° $[\alpha]_D$ +66° (c 1.0;Me_2CO).

Example 95

[2R-[2α(R*),4β,5α]2'R-[2'α(R*),4'β]]-5-Acetoxymethyl-5-methyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-(phenylmethyl)-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

A solution of Intermediate 17 (543mg), 2 β-acetoxypenicillin G (441mg), N-hydroxybenzo-triazole hydrate (197mg) and dicyclohexylcarbodiimide (303mg) in tetrahydrofuran (50ml) was stirred at 21° for 4h. The precipitated solid was filtered off and the filtrate was evaporated to give a foam which was dissolved in ethyl acetate (50ml). The solution was washed with saturated sodium bicarbonate solution and saturated brine, dried and evaporated to give a solid which was triturated with ether to give a white solid. The bulk of this material (881mg) was dissolved in dichloromethane (25ml) containing benzylamine (0.24ml) and left at ca 21° for 3 days. More dichloromethane (25ml) was added and the solution was washed sequentially with N-hydrochloric acid, water, saturated aqueous sodium

bicarbonate and saturated brine solution, then dried and evaporated. The product was purified by flash chromatography on silica gel (Merck Art 9385, 80g) using chloroform-methanol (19:1) to give the title compound (490mg) as a white solid, $[\alpha]_D$ +23.8° (c 1.13; MeOH).

Example 96

[2R-[2α(R*),4β,5α]2'R-[2'α(R*),4'β]]-5-Hydroxymethyl-5-methyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-(phenylmethyl)-α-[(phenylacetyl)amino]-2-thiazolidineacetamide

Saturated methanolic ammonia solution (4ml) was added to a solution of Example 95 (419mg) in methanol (2ml). The solvent was evaporated after 3h and the residue was purified by chromatography on silica gel (Merck 9385, 20g) eluting with chloroform-methanol (19:1) to give a solid which was crystallised from ethyl acetate to give the title compound (51mg), m.p. 131°, $[\alpha]_D$ +54.8° (c 1.05; MeOH).

Example 97

[2R-[2α(R*),4β]]-4-4'-[(2-Hydroxy-1,3-propanediyl)bis(aminocarbonyl)]bis[[5,5-dimethyl-α[(3-methyl-1-oxobutyl)amino]-2-thiazolidineacetamide]]

A solution of Intermediate 44 (200mg) in tetrahydrofuran (10ml) was treated with concentrated (0.88) aqueous ammonia solution (1ml). After 19h the solvent was evaporated and the residue was chromatographed on silica gel (Merck Art 9385, 25g) using chloroform-methanol (19:1 followed by 9:1) then with methanol alone. Appropriate fractions were combined and evaporated. The product was further purified by preparative HPLC (S5-ODS-2-column using aqueous acetonitrile) to give the title compound (33mg), $[\alpha]_D$ +96.4° (c 0.35; Me_2SO), ^1H nmr (DMSO-d_6) δ 0.85 (12H), 1.12 (6H), 1.48 (6H), 1.88-2.05 (6H), 2.83-3.06, 3.10 and 3.33 (4H), 3.47 (2H), 3.54 (1H), 3.72 (2H), 4.32 (2H), 4.85 (2H), 5.01 (1H), 7.05 (2H), 7.32 (2H) and 7.80-7.94 (4H).

Example 98

[2R-[2α(R*),4β]]-4,4'-[(2-Hydroxy-1,3-propanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]

1-Hydroxybenzotriazole monohydrate (190mg) and 1,3-diamino-2-hydroxypropane (51mg) were added successively to a stirred solution of Intermediate 45 (500mg) in dimethylformamide (8ml). After 10 minutes N,N-dicyclohexylcarbodiimide (256mg) was added and the resulting mixture was stirred for 2 hrs. A white solid was removed by filtration and the filtrate was partitioned between ethyl acetate (30ml) and water (100ml). The organic layer was washed successively with 1.0N-hydrochloric acid, water and saturated brine. The dried solution was evaporated to give a white foam (523mg) which was chromatographed on silica gel (Merck 9385, 30g). Elution with chloroform : methanol mixtures varying from 30:1 to 15:1 gave the product as a white powder which crystallised from hot ethyl acetate to afford the title compound (127mg) as white crystals, m.p. 129-132^0,$[\alpha]_D^{20}$ + 73.5^0 (c=0.97 in MeOH), ^{1}H n.m.r. (DMSO-d_6) δ 1.14 (6H), 1.50 (6H), 2.85-3.05 (2H), 3.20-3.40 (2H), 3.48 (2H), 3.50 (4H), 3.55-3.60 (1H), 3.85 (2H), 4.25 (4H), 4.42 (2H), 4.90 (2H), 5.02 (1H), 7.15-7.32 (20H), 7.86 (2H), 8.33 (2H), 8.51 (2H).

Example 99

[2R-[2α(R*),4β(S*)],2'R[2'α(R*),4'β(R*)]]4,4'-[(2,3-Dihydroxy-1,4-butanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]

Sodium hydrogen carbonate (26mg) was added to a stirred solution of Intermediate 46 dihydrochloride (30mg) in water (0.1ml). After 30 min the following were added successively: 1-hydroxybenzotriazole (48mg), tetrahydrofuran (0.5ml), water (0.1ml), Intermediate 45 (138mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (48mg). After a further 2h, more Intermediate 45 (5mg) and the carbodiimide (5mg) were added. After a further $2\frac{1}{2}$hr, the resulting mixture was combined with a similar mixture from another

experiment [the starting materials being Intermediate 46 (100mg), sodium bicarbonate (87mg), Intermediate 45 (459mg), 1-hydroxybenzotriazole hydrate (175mg) and the carbodiimide (199mg) in water (0.6ml) and tetrahydrofuran (2.2ml)] and evaporated to a white foam. Purification was by chromatography on silica gel, with elution by chloroform-methanol mixtures (40:1 to 4:1). Evaporation of appropriate fractions, followed by crystallation from ethanol gave the title compound as a white solid (212mg), mp. 164-167^0,$[\alpha]_D$ + 81^0 (c 1.02, methanol), ^{1}H n.m.r. (DMSO-d_6) δ 1.15 (3H), 1.14 (3H), 1.49 (6H), 3.01-2.84 (1H), ca 3.4-3.12 (4H), 3.71-3.45 (7H), 3.94-3.78 (2H), ca 4.37-4.14 (4H), 4.50 - ca 4.35 (2H), ca 4.95-4.83 (2H), 5.06 - ca 4.95 (2H), 7.35-7.15 (20H), 7.88-7.74 (2H), 8.42-8.29 (2H), 8.58-8.46 (2H).

Example 100

2R-[2α(R*),4β(R*)]-4,4'-[(2,3-Dihydroxy-1,4-butanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]

Sodium hydrogen carbonate (174mg) was added to a stirred solution of Intermediate 47 dihydrochloride (200mg) in water (0.5ml). After 15 min tetrahydrofuran (12ml) was added. After a further 15 min, the following were added successively: Intermediate 45 (1.09g), 1-hydroxybenzotriazole hydrate (349mg) and N,N-dicyclohexylcarbodiimide (470mg). After 24h, the mixture was filtered and the filtrate was evaporated to a white foam. Purification by chromatography on silica-gel, with elution by chloroform-methanol mixtures (80:1 to 20:1), gave the crude product as a white foam. This was crystallised from ethanol to give the title compound as a white solid (160mg),$[\alpha]_D$ + 87^0 (c 1.03 methanol), m.p. 134-138^0, ^{1}H n.m.r. (DMSO-d_6) δ 1.13 (6H), 1.49 (6H), 2.88-3.07 (2H), 3.3-3.60 (6H), 3.52 (4H), 3.76-3.91 (2H), 4.13-4.48 (6H), 4.65-4.55 (2H), 4.83-4.96 (2H), 7.14-7.35 (20H), 7.80-8.13 (2H), 8.31-8.41 (2H), 8.46-8.58 (2H).

Example 101

2R-[2α(R*),4β(S*)]-4,4'-[(2,3-Dihydroxy-1,4-butanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]

1-Hydroxybenzotriazole hydrate (333mg), Intermediate 45 (938mg) and N,N-dicyclohexylcarbodiimide (449mg) were added successively to a solution of Intermediate 48 (200mg) and sodium bicarbonate (174mg) in water (1ml) and tetrahydrofuran (10ml). The resulting mixture was stirred for 16hrs and then filtered. The filtrate was evaporated to dryness and the residue purified by silica gel chromatography (Merck 9385, 120g). Elution with chloroform : methanol mixtures 50:1 → 40:1 → 30:1 → 20:1 → 15:1 → 10:1 gave a white solid which crystallised from hot ethanol to give the title compound (0.53g) as a white powder, mp. 181-183^0,$[\alpha]_D^{20}$ + 69^0 (c = 1.05, MeOH), ^{1}H n.m.r. (DMSO-d_6) δ 1.14 (6H), 1.49 (6H), 3.10-3.30 (4H), 3.45 (2H), 3.50 (6H), 3.85 (2H), 4.27 (4H), 4.43 (2H), 4.68 (2H), 4.90 (2H), 7.15-7.32 (20H), 7.84 (2H), 8.38 (2H), 8.53 (2H).

Example 102

(1) Inhibition of HIV protease activity

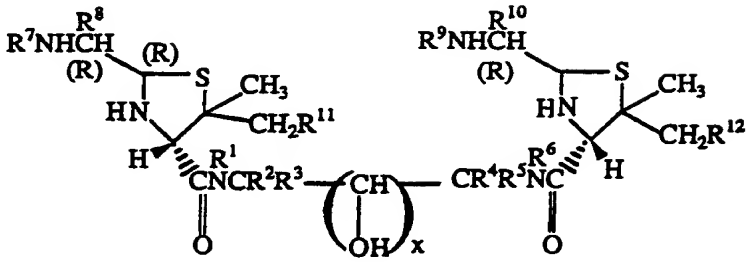
The compounds of the Examples hereinabove were tested following procedures known in the art and were found generally to have EC_{50} values of less than 100nM.

(2) Inhibition of syncytium formation and/or HIV-1 p24 core antigen synthesis

Following the procedures set forth herein the compounds of Examples 1-5, 7-12, 15, 17, 18, 20, 22-26, 29-31, 37, 74-76 and 80 have EC_{50} values within the range of 0.002μM to 0.54μM in one or both of the syncytium formation and antigen synthesis assays.

Claims

1. Compounds of the general formula (I)



(I)

wherein :

x is zero, 1 or 2;

R^1 and R^6 are each independently hydrogen, C_{1-4}alkyl or CH_2C_{1-3}alkyl where the C_{1-3}alkyl portion is substituted by OH;

R^2, R^3, R^4 and R^5 are each independently hydrogen, methyl, ethyl, CH_2OH, CH_2NH_2 or COOH when x is zero, or R^2, R^3, R^4 and R^5 are each independently hydrogen, methyl or CH_2OH when x is 1 or 2;

R^7 and R^9 are each independently hydrogen, C_{1-10}alkyl, C_{3-8}cycloalkyl, ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, COAr, COHet, $COCH_2R^{13}$, COCH(OH)Ar, COCH(OH)Het, COCH=CHPh, COR^{14}, CO_2CH_2Ar, CO_2CH_2Het, SO_2Ar, SO_2Het, $SO_2CH_2R^{15}$, $SO_2CH=CHPh$ or SO_2R^{16} [where R^{13} and R^{15} each independently represent hydrogen, C_{1-6}alkyl, aryl, heteroaryl, ArC_{1-4}alkyl, $HetC_{1-4}$alkyl, aryloxy, heteroaryloxy, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, $(CH_2)_nCO_2R^{17}$ (where n is zero or 1 and R^{17} is hydrogen or C_{1-6}alkyl), $(CH_2)_mNR^{18}R^{19}$ (where m is zero, 1, 2, 3, 4 or 5 and R^{18} and R^{19} are each independently hydrogen or C_{1-4}alkyl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group), and R^{14} and R^{16} each independently represent C_{3-8}cycloalkyl substituted by phenyl];

R^8 and R^{10} are each independently hydrogen, C_{1-6}alkyl, $COOR^{20}$ (where R^{20} is hydrogen, C_{1-6}alkyl or ArC_{1-4}alkyl) or $CONR^{21}R^{22}$ [where R^{21} is

hydrogen or C_{1-4}alkyl and R^{22} is hydrogen, OH, aryl, heteroaryl, ArC_{1-4}alkyl (wherein the C_{1-4}alkyl portion is optionally substituted by hydroxymethyl), $HetC_{1-4}$alkyl, C_{3-8}cycloalkyl, C_{3-8}cycloalkylC_{1-4}alkyl, $(CH_2)_pR^{23}$ (where p is zero or 1 and R^{23} is CF_3 or CO_2R^{24} where R^{24} is hydrogen or C_{1-6}alkyl), $(CH_2)qNR^{25}R^{26}$ (where q is zero, 1, 2, 3, 4 or 5 and R^{25} and R^{26} are each independently hydrogen, C_{1-4}alkyl or aryl or together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group), $CHArCO_2R^{27}$, $CHHetCO_2R^{28}$ (where R^{27} and R^{28} are each independently hydrogen or C_{1-6}alkyl) or C_{1-6}alkyl optionally substituted by OH, or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a saturated heterocyclic amino group];

R^{11} and R^{12} are each independently hydrogen, hydroxy or acetoxy;

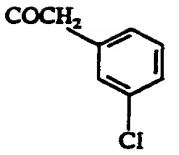
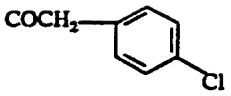
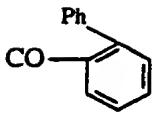
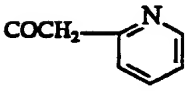
and physiologically acceptable salts and solvates thereof.

2. Compounds according to Claim 1 wherein R^1 and R^6 are hydrogen atoms or methyl groups and R^3, R^4 and R^5 are hydrogen atoms.

3. Compounds according to Claim 1 or Claim 2 wherein R^2 is a hydrogen atom or a methyl, CH_2OH or COOH group when x is zero, and R^2 is a hydrogen atom when x is 1 or 2.

4. Compounds according to any one of Claims 1 to 3 wherein R^7 and R^9 are each independently a group selected from COAr (where Ar is biphenyl), $COCH_2R^{13}$ (where R^{13} is C_{1-6}alkyl, aryl, heteroaryl aryloxy or ArC_{1-4}alkyl) or COR^{14} (where R^{14} is cyclopropyl substituted by phenyl).

5. Compounds according to any one of claims 1 to 3 wherein R^7 and R^9 are each independently $COCH_2Ph$,

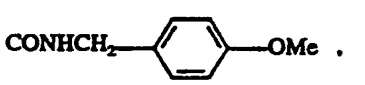
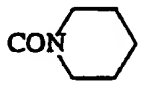
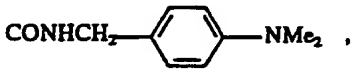
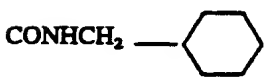
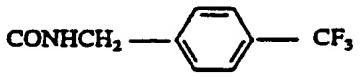
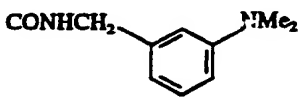
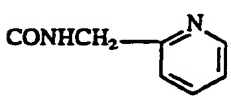
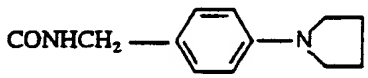

, $COCH_2OPh$, $CO(CH_2)_2Ph$ or

$COCH_2Pr\text{-}i$.

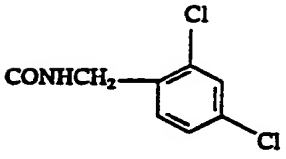
6. Compounds according to any one of Claims 1 to 5 wherein R^8 and R^{10} are each independently a group $CONR^{21}R^{22}$.

7. Compounds according to Claim 6 wherein R^{21} is hydrogen and R^{22} is a group selected from $ArC_{1-4}alkyl$, $HetC_{1-4}alkyl$, $C_{3-8}cycloalkylmethyl$ or CH_2CF_3 or R^{21} is hydrogen or methyl and R^{22} is methyl or ethyl or R^{21} and R^{22} together with the nitrogen atom to which they are attached form a piperidino group.

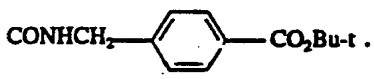
8. Compounds according to any one of Claim 1 to 5 wherein R^8 and R^{10} are each independently $CONHCH_2Ph$, $CONHCH_2CH_3$, $CONHCH_2CH_2Ph$, $CONMe_2$,

, $CONHCH_2CF_3$,



or



9. A compound according to Claim 1 selected from:

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(2,2,2-trifluoroethyl)-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(2-phenylethyl)-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(3-methyl-1-oxobutyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-[(4-methoxyphenyl)methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-Ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-dimethyl-4-[[[[[[5,5-dimethyl-2-[2- oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-α-[(2-phenyl-1-oxoethyl)amino]-N-[(2-pyridinyl)methyl]-2-thiazolidineacetamide;

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-dimethyl-4-[[[[[[5,5-dimethyl-2-[2- oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-(phenylmethyl)-α-[[1-oxo-2-(2-pyridinyl)ethyl]amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5- dimethyl-α-[[[(1,1'-biphenyl)-2-yl]carbonyl]amino]-N-phenylmethyl-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-[(2,4-dichlorophenyl)methyl]-5,5-dimethyl-α-[(2-pyridinylacetyl)amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[[(4-dimethylamino)phenyl]methyl]-α[(phenylacetyl)amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[(N-methylamino) carbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-N-(phenylmethyl)-α-[[[(1,1'-biphenyl)-2-yl]carbonyl] amino]-2-thiazolidine acetamide]];

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-N-[(2,4-dichlorophenyl)methyl]-5,5-dimethyl-4-[[[[[[5,5,-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl] amino]ethyl] amino]carbonyl]-α-[[1-oxo-2-(2-pyridinyl)ethyl]amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-α-[[2-(4-chlorophenyl)-1-oxoethyl]amino]-5,5-dimethyl]-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[(2-pyridinyl)methyl]-2-thiazolidineacetamide;

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[[(2-phenylcyclopropyl)carbonyl]amino]-N-(phenylmethyl)-2-thiazolidineacetamide]] (Isomer B);

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[[(3-dimethylamino)phenyl]methyl]-α-[(phenylacetyl) amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[α-[[(3-chloro)phenylacetyl]amino]-N-ethyl-5,5-dimethyl-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[(4-(((1,1-dimethyl)ethoxy)carbonyl)phenyl)methyl]-α-[(2-phenyl-1-oxoethyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β(R*S*)],2'R-[2'α(R*),4'β]]-4,4'-[(1-methyl-1,2-ethanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl) amino]-N-(phenylmethyl)-2-thiazolidineacetamide];

[2R-[2α(R*),4β(R*)],2'R-[2'α(R*),4'β]]-4,4'-[(1-methyl-1,2-ethanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide];

[2R-[2α(R*),4β(R*,S*)],2'R-[2'α(R*),4'β]]-4,4'-[(1-hydroxymethyl-1,2-ethanediyl)bis(aminocarbonyl)]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-(phenylmethyl)-2-thiazolidineacetamide];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-[(4-(1-pyrrolidinyl)phenyl) methyl]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-N-[[(4-dimethylamino)phenyl]methyl]-α-[[[(1,1'-biphenyl-2-yl]carbonyl]amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]2'R-[2'α(R*),4'β]]-5,5-dimethyl-4-[[[[[[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-[(phenylmethyl)amino]ethyl]-4-thiazolidinyl]carbonyl]amino]ethyl]amino]carbonyl]-N-[[4-(dimethylamino)phenyl]methyl]-α-[(phenylacetyl)amino]-2-thiazolidineacetamide;

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N,N-dimethyl-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-1,2-[ethanediylbis[aminocarbonyl]bis[N-(cyclohexylmethyl)-5,5-dimethyl-α-[(phenylacetyl)amino]-2-thiazoleacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[5,5-dimethyl-α-[(phenylacetyl)amino]-N-[(4-(trifluoromethyl) phenyl)methyl]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-N,N'-[1,2-ethanediylbis[5,5-dimethyl-2-[2-oxo-1-[(phenylacetyl)amino]-2-(1-piperidinyl)ethyl]-4-thiazolidinecarboxamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(3-phenyl-1-oxopropyl)amino]-2-thiazolidineacetamide]];

[2R-[2α(R*),4β]]-4,4'-[1,2-ethanediylbis[aminocarbonyl]bis[N-ethyl-5,5-dimethyl-α-[(phenoxyacetyl)amino]-2-thiazolidineacetamide]];

or a physiologically acceptable salt or solvate thereof.

10. A compound according to any one of Claims 1 to 9 or a physiologically acceptable salt or solvate thereof for use as a therapeutically active agent.

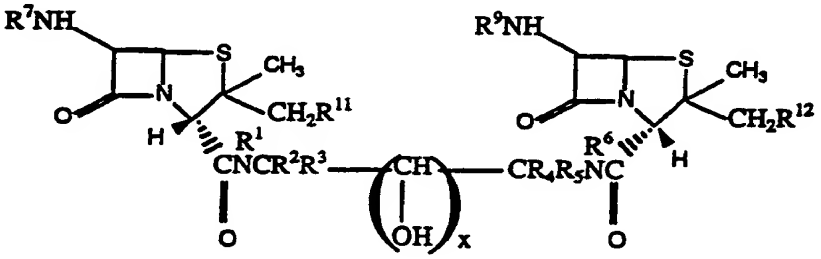
11. A compound according to any one of Claims 1 to 9 or a physiologically acceptable salt or solvate thereof for use in the treatment of a viral infection.

12. Use of a compound according to any one of Claims 1 to 9 or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of a retroviral infection.

13. A pharmaceutical formulation comprising a compound according to any one of Claims 1 to 9 or a physiologically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers.

14. A process for preparing a compound according to Claim 1 or a physiologically acceptable salt or solvate thereof, which comprises:

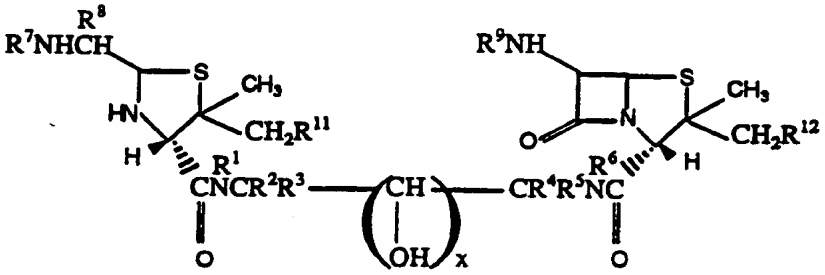
(A) in preparing compounds in which R^8 and R^{10} represent $COOR^{20}$ or $CONR^{21}R^{22}$, treating compounds of formula (II)



(II)

or protected derivatives thereof with a nucleophile $R^{20}OH$ or $R^{21}R^{22}NH$, followed, where necessary, by the removal of any protecting groups present;

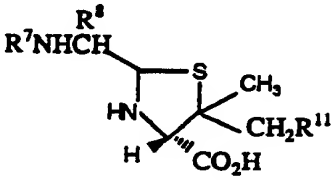
(B) in preparing compounds in which R^{10} represents $COOR^{20}$ or $CONR^{21}R^{22}$, treating compounds of formula (III)



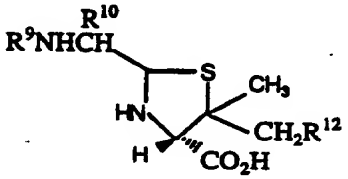
(III)

or protected derivatives thereof with a nucleophile $R^{20}OH$ or $R^{21}R^{22}NH$, followed, where necessary, by the removal of any protecting groups present;

(C) coupling the carboxylic acids of formulae (IV) and (V)

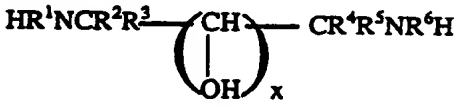


(IV)



(V)

or salts and/or protected derivatives thereof with a diamine of formula (VI)



(VI)

or a protected derivative thereof, followed, where necessary, by the removal of any protecting groups present; or

(D) interconverting compounds of formula (I);

and if necessary or desired subjecting the compounds resulting from any of steps (A) to (D) above to a further reaction comprising: converting a compound of formula (I) or a salt thereof into a physiologically acceptable salt thereof.

15. Compounds of formulae (II), (III) and (IX).

16. A method for the treatment of a viral infection in a mammal comprising administering to said mammal a therapeutically effective amount of a compound as claimed in Claim 1 or a physiologically acceptable salt or solvate thereof.

17. A pharmaceutical formulation comprising a compound according to any one of Claims 1 to 9 or a physiologically acceptable salt or solvate thereof for use in the treatment of a viral infection in a mammal.

18. Compounds according to any one of Claims 1 to 9 substantially as herein described.

19. Compositions according to Claim 13 or Claim 17 substantially as herein described.

International Application No PCT/GB 92/00840

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 277/06 A 61 K 31/425 C 07 D 417/12
C 07 D 499/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0346847 (F. HOFFMANN-LA ROCHE) 20 December 1989, see claims; pages 13,14,36,37 ---	1,12,13 ,16,17, 19
A	Journal of Medicinal Chemistry, vol. 33, no. 10, October 1990, (Washington, DC, US), R.B. GAMMILL et al.: "Structure-based, C2 symmetric inhibitors of HIV protease", pages 2687-2689 ---	
A	Journal of Medicinal Chemistry, vol. 33, no. 5, May 1990, (Washington, DC, US), D.H. RICH et al.: "Hydroxyethylamine analogues of the p17/p24 substrate cleavage site are tight-binding inhibitors of HIV protease", pages 1285-1288 -----	

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03-08-1992	18. 09. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Nicolas Wellberg

INTERNATIONAL SEARCH REPORT | P '/GB92/00840

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 11,16 are directed to a method of treatment of the human body the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9200840 SA 59203

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/08/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0346847	20-12-89	AU-A- 3613089	14-12-89
		JP-A- 2042048	13-02-90